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(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

11729.1 contg

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11729-45.21.21.cons2

11731.lcont1g

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as ovarian cancer, are disclosed. Compositions may comprise one or more ovarian carcinoma proteins, immunogenic portions thereof, polynucleotides that encode such portions or antibodies or immune system cells specific for such proteins. Such compositions may be used, for example, for the prevention and treatment of diseases such as ovarian cancer. Methods are further provided for identifying tumor antigens that are secreted from ovarian carcinomas and/or other tumors. Polypeptides and polynucleotides as provided herein may further be used for the diagnosis and monitoring of ovarian cancer.



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COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

Technical Field

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The present invention relates generally to ovarian cancer therapy. The invention is more specifically related to polypeptides comprising at least a portion of an ovarian carcinoma protein, and to polynucleotides encoding such polypeptides, as well as antibodies and immune system cells that specifically recognize such polypeptides. Such polypeptides, polynucleotides, antibodies and cells may be used in vaccines and pharmaceutical compositions for treatment of ovarian cancer.

10 Background of the Invention

Ovarian cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and therapy of this cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Management of the disease currently relies on a combination of early diagnosis and aggressive treatment, which may include one or more of a variety of treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. However, the use of established markers often leads to a result that is difficult to interpret, and high mortality continues to be observed in many cancer patients.

Immunotherapies have the potential to substantially improve cancer treatment and survival. Such therapies may involve the generation or enhancement of an immune response to an ovarian carcinoma antigen. However, to date, relatively few ovarian carcinoma antigens are known and the generation of an immune response against such antigens has not been shown to be therapeutically beneficial.

Accordingly, there is a need in the art for improved methods for identifying ovarian tumor antigens and for using such antigens in the therapy of ovarian cancer. The present invention fulfills these needs and further provides other related advantages.

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SUMMARY OF THE INVENTION

Briefly stated, this invention provides compositions and methods for the therapy of cancer, such as ovarian cancer. In one aspect, the present invention provides polypeptides comprising an immunogenic portion of an ovarian carcinoma protein, or a 5 variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma proteinspecific antisera is not substantially diminished. Within certain embodiments, the ovarian carcinoma protein comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:456-457, 460-477 and 512-570 and complements of such polynucleotides.

The present invention further provides polynucleotides that encode a polypeptide as described above or a portion thereof, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences recited in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596.

Within other aspects, the present invention provides pharmaceutical Pharmaceutical compositions may comprise a compositions and vaccines. physiologically acceptable carrier or excipient in combination with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma proteinspecific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570 or (ii) a polynucleotide encoding such a polypeptide; (iii) an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide. Vaccines may comprise a non-specific immune response enhancer in combination with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions

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and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence set forth in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596 or an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570 or (ii) a polynucleotide encoding such a polypeptide; (iii) an anti-idiotypic antibody that is specifically bound by an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for 20 inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for stimulating and/or expanding T cells, comprising contacting T cells with (a) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence set forth in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596 or an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570; (b) a polynucleotide encoding such a polypeptide and/or (c) an antigen presenting cell that

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expresses such a polypeptide under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Such polypeptide, polynucleotide and/or antigen presenting cell(s) may be present within a pharmaceutical composition or vaccine, for use in stimulating and/or expanding T cells in a mammal.

Within other aspects, the present invention provides methods for inhibiting the development of ovarian cancer in a patient, comprising administering to a patient T cells prepared as described above.

Within further aspects, the present invention provides methods for inhibiting the development of ovarian cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570; (ii) a polynucleotide encoding such a polypeptide; or (iii) an antigen-presenting cell that expresses such a polypeptide; such that T cells proliferate; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of ovarian cancer in the patient. The proliferated cells may be cloned prior to administration to the patient.

The present invention also provides, within other aspects, methods for identifying secreted tumor antigens. Such methods comprise the steps of: (a) implanting tumor cells in an immunodeficient mammal; (b) obtaining serum from the immunodeficient mammal after a time sufficient to permit secretion of tumor antigens into the serum; (c) immunizing an immunocompetent mammal with the serum; (d) obtaining antiserum from the immunocompetent mammal; and (e) screening a tumor expression library with the antiserum, and therefrom identifying a secreted tumor antigen. A preferred method for identifying a secreted ovarian carcinoma antigen comprises the steps of: (a) implanting ovarian carcinoma cells in a SCID mouse; (b) obtaining serum from the SCID mouse after a time sufficient to permit secretion of

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ovarian carcinoma antigens into the serum; (c) immunizing an immunocompetent mouse with the serum; (d) obtaining antiserum from the immunocompetent mouse; and (e) screening an ovarian carcinoma expression library with the antiserum, and therefrom identifying a secreted ovarian carcinoma antigen.

The present invention also discloses antibody epitopes recognized by the O8E polyclonal anti-sera which epitopes are presented herein as SEQ ID NO: 394-415.

Further disclosed by the present invention are 10-mer and 9-mer peptides predicted to bind HLA-0201 which peptides are disclosed herein as SEQ ID NO:416-435 and SEQ ID NO:436-455, respectively.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

In another aspect of the present invention, the applicants have unexpectedly identified a series of novel repeating sequence elements in the 5' end of the gene encoding O772P. Therefore, the present invention provides O772P polypeptides having structures represented by X_n-Y, wherein X comprises a sequence having at least 50% identity, preferably at least 70% identity, and more preferably at least 90% identity with an O772P repeat sequence set forth in SEQ ID NO: 596. Y will typically comprise a sequence having at least 80% identity, preferably at least 90% identity and more preferably at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 594. According to this embodiment, n will generally be an integer from 1 to 35, preferably an integer from 15 to 25, and X can be the same or different.

In one preferred embodiment, X comprises a sequence selected from the group consisting of any one of SEQ ID NOs: 574-593 and Y comprises the sequence set forth in SEQ ID NO: 594.

In another preferred embodiment, an illustrative O772P polypeptide comprises the sequence set forth in SEQ ID NO: 595, containing 20 repeating sequence elements (i.e., X₂₀) wherein the X elements are arranged in the following order (moving from N-terminal to C-terminal in the O772P repeat region): SEQ ID NO: 574 - SEQ ID



NO: 575 - SEQ ID NO: 576 - SEQ ID NO: 577 - SEQ ID NO: 578 - SEQ ID NO: 579 - SEQ ID NO: 580 - SEQ ID NO: 581 - SEQ ID NO: 582 - SEQ ID NO: 583 - SEQ ID NO: 584 - SEQ ID NO: 585 - SEQ ID NO: 586 - SEQ ID NO: 587 - SEQ ID NO: 588 - SEQ ID NO: 589 - SEQ ID NO: 590 - SEQ ID NO: 591 - SEQ ID NO: 592 - SEQ ID NO: 593.

According to another aspect of the present invention, an O772P polynucleotide is provided having the structure X_n -Y, wherein X comprises an O772P repeat sequence element selected from the group consisting of any one of SEQ ID NOs: 512-540, 542-546 and 548-567. Y will generally comprise a sequence having at least 80% identity, preferably at least 90% identity, and more preferably at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 568. In this embodiment, n is typically an integer from 1 to 35, preferably from 15 to 25 and X can be the same or different.

In another embodiment, an illustrative O772P polynucleotide comprises the sequence set forth in SEQ ID NO: 569, containing 20 repeating sequence elements (i.e., X_{20}).

According to another aspect of the present invention, O772 polypeptides are provided comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 490-511.

According to another aspect of the present invention, O8E polypeptides are provided comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 394-415.

BRIEF DESCRIPTION OF THE SEQUENCE IDENTIFIERS AND DRAWINGS

SEQ ID NO:1-71 are ovarian carcinoma antigen polynucleotides shown 25 in Figures 1A-1S.

SEQ ID NO:72-74 are ovarian carcinoma antigen polynucleotides shown in Figures 2A-2C.

SEQ ID NO:75 is the ovarian carcinoma polynucleotide 3g (Figure 4).

SEQ ID NO:76 is the ovarian carcinoma polynucleotide 3f (Figure 5).

SEQ ID NO:77 is the ovarian carcinoma polynucleotide 6b (Figure 6).

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SEQ ID NO:78 is the ovarian carcinoma polynucleotide 8e (Figure 7A).

SEQ ID NO:79 is the ovarian carcinoma polynucleotide 8h (Figure 7B).

SEQ ID NO:80 is the ovarian carcinoma polynucleotide 12e (Figure 8).

SEQ ID NO:81 is the ovarian carcinoma polynucleotide 12h (Figure 9).

SEQ ID NO:82-310 are ovarian carcinoma antigen polynucleotides shown in Figures 15A-15EEE.

SEQ ID NO:311 is a full length sequence of ovarian carcinoma polynucleotide O772P.

SEQ ID NO:312 is the O772P amino acid sequence.

SEQ ID NO:313-384 are ovarian carcinoma antigen polynucleotides.

SEQ ID NO:385 represents the cDNA sequence of a form of the clone O772P, designated 21013.

SEQ ID NO:386 represents the cDNA sequence of a form of the clone O772P, designated 21003.

SEQ ID NO:387 represents the cDNA sequence of a form of the clone O772P, designated 21008.

SEQ ID NOs:388 is the amino acid sequence corresponding to SEQ ID NO:385.

SEQ ID NOs:389 is the amino acid sequence corresponding to SEQ ID NO:386.SEQ ID NOs:390 is the amino acid sequence corresponding to SEQ ID NO:387.

SEQ ID NO:391 is a full length sequence of ovarian carcinoma polynucleotide O8E.

SEQ ID NO:392-393 are protein sequences encoded by O8E.

SEQ ID NO:394-415 are peptide sequences corresponding to the OE8 antibody epitopes.

SEQ ID NO:416-435 are potential HLA-A2 10-mer binding peptides predicted using the full length open-reading frame from OE8.

SEQ ID NO:436-455 are potential HLA-A2 9-mer binding peptides predicted using the full length open-reading frame from OE8.

SEQ ID NO:456 is a truncated nucleotide sequence of the full length Genbank sequence showing homology to O772P

SEQ ID NO:457 is the full length Genbank sequence showing significant homology to O772P

5 SEQ ID NO:458 is a protein encoding a truncated version of the full length Genbank sequence showing homology to O772P

SEQ ID NO:459 is the full length protein sequence from Genbank showing significant homology to the protein sequence for O772P

SEQ ID NO:460 encodes a unique N-terminal portion of O772P contained in residues 1-70.

SEQ ID NO:461 contains unique sequence and encodes residues 1-313 of SEQ ID NO: 456.

SEQ ID NO:462 is the hypothetical sequence for clone O772P.

SEQ ID NO:463 is the cDNA sequence for clone FLJ14303.

15 SEQ ID NO:464 is a partial cDNA sequence for clone O772P.

SEQ ID NO:465 is a partial cDNA sequence for clone O772P.

SEQ ID NO:466 is a partial cDNA sequence for clone O772P.

SEQ ID NO:467 is a partial cDNA sequence for clone O772P.

SEQ ID NO:468 is a partial cDNA sequence for clone O772P.

SEQ ID NO:469 is a partial cDNA sequence for clone O772P.

SEQ ID NO:470 is a partial cDNA sequence for clone O772P.

SEQ ID NO:471 is a partial cDNA sequence for clone O772P.

SEQ ID NO:472 is a partial cDNA sequence for clone O772P.

SEQ ID NO:473 is a partial cDNA sequence for clone O772P.

SEQ ID NO:474 is a partial cDNA sequence for clone O772P.

SEQ ID NO:475 is a partial cDNA sequence for clone O772P.

SEQ ID NO:476 is a partial cDNA sequence for clone O772P.

SEQ ID NO:477 represents the novel 5'-end of the ovarian tumor antigen

0772P.

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SEQ ID NO:478 is the amino acid sequence encoded by SEQ ID NO:462.

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SEQ ID NO:479 is the amino acid sequence encoded by SEQ ID NO:463.

SEQ ID NO:480 is a partial amino acid sequence encoded by SEQ ID NO:472.

SEQ ID NO:481 is a partial amino acid sequence encoded by a possible open reading frame of SEQ ID NO:471.

SEQ ID NO:482 is a partial amino acid sequence encoded by a second possible open reading frame of SEQ ID NO:471.

SEQ ID NO:483 is a partial amino acid sequence encoded by SEQ ID NO:467. 10

SEQ ID NO:484 is a partial amino acid sequence encoded by a possible open reading frame of SEQ ID NO:466.

SEQ ID NO:485 is a partial amino acid sequence encoded by a second possible open reading frame of SEQ ID NO:466.

SEQ ID NO:486 is a partial amino acid sequence encoded by SEQ ID NO:465.

SEQ ID NO:487 is a partial amino acid sequence encoded by SEQ ID NO:464.

SEQ ID NO:488 represents the extracellular, transmembrane and cytoplasmic regions of O772P. 20

SEQ ID NO:489 represents the predicted extracellular domain of O772P.

SEQ ID NO:490 represents the amino acid sequence of peptide #2 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:491 represents the amino acid sequence of peptide #6 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:492 represents the amino acid sequence of peptide #7 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:493 represents the amino acid sequence of peptide #8 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:494 represents the amino acid sequence of peptide #9 which 30 corresponds to an O772P specific antibody epitope.

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SEQ ID NO:495 represents the amino acid sequence of peptide #11 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:496 represents the amino acid sequence of peptide #13 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:497 represents the amino acid sequence of peptide #22 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:498 represents the amino acid sequence of peptide #24 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:499 represents the amino acid sequence of peptide #27 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:500 represents the amino acid sequence of peptide #40 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:501 represents the amino acid sequence of peptide #41 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:502 represents the amino acid sequence of peptide #47 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:503 represents the amino acid sequence of peptide #50 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:504 represents the amino acid sequence of peptide #51 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:505 represents the amino acid sequence of peptide #52 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:506 represents the amino acid sequence of peptide #53 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:507 represents the amino acid sequence of peptide #58 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:508 represents the amino acid sequence of peptide #59 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:509 represents the amino acid sequence of peptide #60 which corresponds to an O772P specific antibody epitope.

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SEQ ID NO:510 represents the amino acid sequence of peptide #61 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:511 represents the amino acid sequence of peptide #71 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:512 (O772P repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:513 (O772P repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:514 (O772P repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:515 (O772P repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:516 (O772P repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:517 (HB repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:518 (HB repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:519 (HB repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:520 (HB repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:521 (HB repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:522 (HB repeat6 5'-end) represents an example of a cDNA sequence corresponding to repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:523 (1043400.1 repeat1) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:524 (1043400.1 repeat2) represents an example of a cDNA sequence corresponding to repeat number 10 from the 5' variable region of O772P.

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SEQ ID NO:525 (1043400.1 repeat3) represents an example of a cDNA sequence corresponding to repeat number 10/11 from the 5' variable region of O772P. SEQ ID NO:526 (1043400.1 repeat4) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P. 5 SEQ ID NO:527 (1043400.1 repeat5) represents an example of a cDNA sequence corresponding to repeat number 14 from the 5' variable region of O772P. SEQ ID NO:528 (1043400.1 repeat6) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P. SEQ ID NO:529 (1043400.3 repeat1) represents an example of a cDNA 10 sequence corresponding to repeat number 20 from the 5' variable region of O772P. SEQ ID NO:530 (1043400.3 repeat2) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P. SEQ ID NO:531 (1043400.5 repeat1) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P. 15 SEQ ID NO:532 (1043400.5 repeat2) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P, in addition containing intron sequence. SEQ ID NO:533 (1043400.5 repeat2) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P. 20 SEQ ID NO:534 (1043400.8 repeat1) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P. SEQ ID NO:535 (1043400.8 repeat2) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P. SEQ ID NO:536 (1043400.8 repeat3) represents an example of a cDNA 25 sequence corresponding to repeat number 19 from the 5' variable region of O772P. SEQ ID NO:537 (1043400.9 repeat1) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P. SEQ ID NO:538 (1043400.9 repeat2) represents an example of a cDNA

30 SEQ ID NO:539 (1043400.9 repeat3) represents an example of a cDNA sequence corresponding to repeat number 7 from the 5' variable region of O772P.

sequence corresponding to repeat number 5 from the 5' variable region of O772P.



SEQ ID NO:540 (1043400.9 repeat4) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P. SEQ ID NO:541 (1043400.11 repeat1) represents an example of a cDNA sequence corresponding to repeat number 1 from the 5' variable region of O772P. SEQ ID NO:542 (1043400.11 repeat2) represents an example of a cDNA 5 sequence corresponding to repeat number 2 from the 5' variable region of O772P. SEQ ID NO:543 (1043400.11 repeat3) represents an example of a cDNA sequence corresponding to repeat number 3 from the 5' variable region of O772P. SEQ ID NO:544 (1043400.11 repeat4) represents an example of a cDNA 10 sequence corresponding to repeat number 11 from the 5' variable region of O772P. SEQ ID NO:545 (1043400.11 repeat5) represents an example of a cDNA sequence corresponding to repeat number 12 from the 5' variable region of O772P. SEQ ID NO:546 (1043400.12 repeat1) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P. SEQ ID NO:547 (PB repeatA) represents an example of a cDNA 15 sequence corresponding to repeat number 1 from the 5' variable region of O772P. SEQ ID NO:548 (PB repeatB) represents an example of a cDNA sequence corresponding to repeat number 2 from the 5' variable region of O772P. SEQ ID NO:549 (PB repeatE) represents an example of a cDNA sequence corresponding to repeat number 3 from the 5' variable region of O772P. 20 SEQ ID NO:550 (PB repeatG) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P. SEQ ID NO:551 (PB repeatC) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P. SEQ ID NO:552 (PB repeatH) represents an example of a cDNA 25 sequence corresponding to repeat number 6 from the 5' variable region of O772P. SEQ ID NO:553 (PB repeatJ) represents an example of a cDNA sequence corresponding to repeat number 7 from the 5' variable region of O772P. SEQ ID NO:554 (PB repeatK) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P. 30

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SEQ ID NO:555 (PB repeatD) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:556 (PB repeatl) represents an example of a cDNA sequence corresponding to repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:557 (PB repeatM) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:558 (PB repeat9) represents an example of a cDNA sequence corresponding to repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:559 (PB repeat8.5) represents an example of a cDNA sequence corresponding to repeat number 13 from the 5' variable region of O772P.

SEQ ID NO:560 (PB repeat8) represents an example of a cDNA sequence corresponding to repeat number 14 from the 5' variable region of O772P.

SEQ ID NO:561 (PB repeat7) represents an example of a cDNA sequence corresponding to repeat number 15 from the 5' variable region of O772P.

SEQ ID NO:562 (PB repeat6) represents an example of a cDNA sequence corresponding to repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:563 (PB repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:564 (PB repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:565 (PB repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:566 (PB repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:567 (PB repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:568 represents the cDNA sequence form the 3' constant region.

SEQ ID NO:569 represents a cDNA sequence containing the consensus sequences of the 21 repeats, the 3' constant region and the 3' untranslated region.

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SEQ ID NO:570 represents the cDNA sequence of the consensus repeat sequence.

SEQ ID NO:571 represents the consensus amino acid sequence of one potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:572 represents the consensus amino acid sequence of a second potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:573 represents the consensus amino acid sequence of a third potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:574 represents the consensus amino acid sequence of repeat number 2 from the 5' variable region of O772P.

SEQ ID NO:575 represents the consensus amino acid sequence of repeat number 3 from the 5' variable region of O772P.

SEQ ID NO:576 represents the consensus amino acid sequence of repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:577 represents the consensus amino acid sequence of repeat number 5 from the 5' variable region of O772P.

SEQ ID NO:578 represents the consensus amino acid sequence of repeat number 6 from the 5' variable region of O772P.

SEQ ID NO:579 represents the consensus amino acid sequence of repeat number 7 from the 5' variable region of O772P.

SEQ ID NO:580 represents the consensus amino acid sequence of repeat number 8 from the 5' variable region of O772P.

SEQ ID NO:581 represents the consensus amino acid sequence of repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:582 represents the consensus amino acid sequence of repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:583 represents the consensus amino acid sequence of repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:584 represents the consensus amino acid sequence of repeat number 12 from the 5' variable region of O772P.

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SEQ ID NO:585 represents the consensus amino acid sequence of repeat number 13 from the 5' variable region of O772P.

SEQ ID NO:586 represents the consensus amino acid sequence of repeat number 14 from the 5' variable region of O772P.

5 SEQ ID NO:587 represents the consensus amino acid sequence of repeat number 15 from the 5' variable region of O772P.

SEQ ID NO:588 represents the consensus amino acid sequence of repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:589 represents the consensus amino acid sequence of repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:590 represents the consensus amino acid sequence of repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:591 represents the consensus amino acid sequence of repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:592 represents the consensus amino acid sequence of repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:593 represents the consensus amino acid sequence of repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:594 represents the amino acid sequence of the 3' constant 20 region.

SEQ ID NO:595 represents an amino acid sequence containing the consensus sequences of the 21 repeats and the 3' constant region.

SEQ ID NO:596 represents the amino acid sequence of the consensus repeat sequence.

Figures 1A-1S (SEQ ID NO:1-71) depict partial sequences of polynucleotides encoding representative secreted ovarian carcinoma antigens.

Figure 2A-2C depict full insert sequences for three of the clones of Figure 1. Figure 2A shows the sequence designated O7E (11731; SEQ ID NO:72), Figure 2B shows the sequence designated O9E (11785; SEQ ID NO:73) and Figure 2C shows the sequence designated O8E (13695; SEQ ID NO:74).

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Figure 3 presents results of microarray expression analysis of the ovarian carcinoma sequence designated O8E.

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Figure 4 presents a partial sequence of a polynucleotide (designated 3g; SEQ ID NO:75) encoding an ovarian carcinoma sequence that is a splice fusion between the human T-cell leukemia virus type I oncoprotein TAX and osteonectin.

Figure 5 presents the ovarian carcinoma polynucleotide designated 3f (SEQ ID NO:76).

Figure 6 presents the ovarian carcinoma polynucleotide designated 6b (SEQ ID NO:77).

Figures 7A and 7B present the ovarian carcinoma polynucleotides designated 8e (SEQ ID NO:78) and 8h (SEQ ID NO:79).

Figure 8 presents the ovarian carcinoma polynucleotide designated 12c (SEQ ID NO:80).

Figure 9 presents the ovarian carcinoma polynucleotide designated 12h (SEQ ID NO:81).

Figure 10 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 3f.

Figure 11 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 6b.

Figure 12 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 8e.

Figure 13 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 12c.

Figure 14 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 12h.

Figures 15A-15EEE depict partial sequences of additional polynucleotides encoding representative secreted ovarian carcinoma antigens (SEQ ID NO:82-310).

Figure 16 is a diagram illustrating the location of various partial O8E sequences within the full length sequence.

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Figure 17 is a graph illustrating the results of epitope mapping studies on O8E protein.

Figure 18 is graph of a fluorescence activated cell sorting (FACS) analysis of O8E cell surface expression.

Figure 19 is graph of a FACS analysis of O8E cell surface expression.

Figure 20 shows FACS analysis results for O8E transfected HEK293 cells demonstrating cell surface expression of O8E.

Figure 21 shows FACS analysis results for SKBR3 breast tumor cells demonstrating cell surface expression of O8E.

Figure 22 shows 08E expression in HEK 293 cells. The cells were probed with anti-08E rabbit polyclonal antisera #2333L.

Figure 23 shows the ELISA analysis of anti-08E rabbit sera.

Figure 24 shows the ELISA analysis of affinity purified rabbit anti-08E polyclonal antibody.

Figure 25 is a graph determining antibody internalization of anti-O8E mAb showing that mAbs against amino acids 61-80 induces ligand internalization.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy of cancer, such as ovarian cancer. The compositions described herein may include immunogenic polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies that bind to a polypeptide, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells).

Polypeptides of the present invention generally comprise at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof. Certain ovarian carcinoma proteins have been identified using an immunoassay technique, and are referred to herein as ovarian carcinoma antigens. An "ovarian carcinoma antigen" is a protein that is expressed by ovarian tumor cells (preferably human cells) at a level that is at least two fold higher than the level in normal ovarian cells. Certain ovarian carcinoma antigens react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera generated against serum from an immunodeficient animal

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implanted with a human ovarian tumor. Such ovarian carcinoma antigens are shed or secreted from an ovarian tumor into the sera of the immunodeficient animal. Accordingly, certain ovarian carcinoma antigens provided herein are secreted antigens. Certain nucleic acid sequences of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence.

The present invention further provides ovarian carcinoma sequences that are identified using techniques to evaluate altered expression within an ovarian tumor. Such sequences may be polynucleotide or protein sequences. Ovarian carcinoma sequences are generally expressed in an ovarian tumor at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in normal ovarian tissue, as determined using a representative assay provided herein. Certain partial ovarian carcinoma polynucleotide sequences are presented herein. Proteins encoded by genes comprising such polynucleotide sequences (or complements thereof) are also considered ovarian carcinoma proteins.

Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to at least a portion of an ovarian carcinoma polypeptide as described herein. T cells that may be employed within the compositions provided herein are generally T cells (e.g., CD4⁺ and/or CD8⁺) that are specific for such a polypeptide. Certain methods described herein further employ antigen-presenting cells (such as dendritic cells or macrophages) that express an ovarian carcinoma polypeptide as provided herein.

Ovarian Carcinoma Polynucleotides

Any polynucleotide that encodes an ovarian carcinoma protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides, and more preferably at least 45 consecutive nucleotides, that encode a portion of an ovarian carcinoma protein. More preferably, a polynucleotide encodes an immunogenic portion of an ovarian carcinoma protein, such as an ovarian carcinoma antigen. Polynucleotides complementary to any

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such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes an ovarian carcinoma protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native ovarian carcinoma protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native ovarian carcinoma protein or a portion thereof.

The percent identity for two polynucleotide or polypeptide sequences may be readily determined by comparing sequences using computer algorithms well known to those of ordinary skill in the art, such as Megalign, using default parameters. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, or 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Optimal alignment of sequences for comparison may be conducted, for example, using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. Preferably, the percentage of sequence identity is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the window may comprise additions or deletions (i.e., gaps) of 20 % or less, usually 5 to 15 %, or 10 to 12%, relative to the reference sequence (which does not contain additions or

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deletions). The percent identity may be calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e., the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native ovarian carcinoma protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, an ovarian carcinoma polynucleotide may be identified, as described in more detail below, by screening a late passage ovarian tumor expression library with antisera generated against sera of immunocompetent mice after injection of such mice with sera from SCID mice implanted with late passage ovarian tumors. Ovarian carcinoma polynucleotides may also be identified using any of a variety of techniques designed to evaluate differential gene expression. Alternatively, polynucleotides may

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be amplified from cDNA prepared from ovarian tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., an ovarian carcinoma cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with ³²P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target

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sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding portions of ovarian carcinoma antigens are provided in Figures 1A-1S (SEQ ID NO:1 to 71) and Figures 15A to 15EEE (SEQ ID NO:82 to 310). The sequences provided in Figures 1A-1S appear to be novel. For sequences in Figures 15A-15EEE, database searches revealed matches having substantial identity. These polynucleotides were isolated by serological screening of an ovarian tumor cDNA expression library, using a technique designed to identify secreted tumor antigens. Briefly, a late passage ovarian tumor expression library was prepared from a SCID-derived human ovarian tumor (OV9334) in the vector λ-screen (Novagen). The sera used for screening were obtained by

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injecting immunocompetent mice with sera from SCID mice implanted with one late passage ovarian tumors. This technique permits the identification of cDNA molecules that encode immunogenic portions of secreted tumor antigens.

The polynucleotides recited herein, as well as full length polynucleotides comprising such sequences, other portions of such full length polynucleotides, and sequences complementary to all or a portion of such full length molecules, are specifically encompassed by the present invention. It will be apparent to those of ordinary skill in the art that this technique can also be applied to the identification of antigens that are secreted from other types of tumors.

Other nucleic acid sequences of cDNA molecules encoding portions of ovarian carcinoma proteins are provided in Figures 4-9 (SEQ ID NO:75-81), as well as SEQ ID NO:313-384. These sequences were identified by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in an ovarian tumor than in normal ovarian tissue, as determined using a representative assay provided herein). Such screens were performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). SEQ ID NO:311 and 391 provide full length sequences incorporating certain of these nucleic acid sequences.

Any of a variety of well known techniques may be used to evaluate tumor-associated expression of a cDNA. For example, hybridization techniques using labeled polynucleotide probes may be employed. Alternatively, or in addition, amplification techniques such as real-time PCR may be used (see Gibson et al., Genome Research 6:995-1001, 1996; Heid et al., Genome Research 6:986-994, 1996). Real-time PCR is a technique that evaluates the level of PCR product accumulation during amplification. This technique permits quantitative evaluation of mRNA levels in multiple samples. Briefly, mRNA is extracted from tumor and normal tissue and cDNA is prepared using standard techniques. Real-time PCR may be performed, for example, using a Perkin Elmer/Applied Biosystems (Foster City, CA) 7700 Prism instrument. Matching primers and fluorescent probes may be designed for genes of interest using, for example, the primer express program provided by Perkin Elmer/Applied Biosystems

(Foster City, CA). Optimal concentrations of primers and probes may be initially determined by those of ordinary skill in the art, and control (e.g., β-actin) primers and probes may be obtained commercially from, for example, Perkin Elmer/Applied Biosystems (Foster City, CA). To quantitate the amount of specific RNA in a sample, a standard curve is generated alongside using a plasmid containing the gene of interest. Standard curves may be generated using the Ct values determined in the real-time PCR, which are related to the initial cDNA concentration used in the assay. Standard dilutions ranging from 10-10⁶ copies of the gene of interest are generally sufficient. In addition, a standard curve is generated for the control sequence. This permits standardization of initial RNA content of a tissue sample to the amount of control for comparison purposes.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding an ovarian carcinoma antigen, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo.

A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression.

25 cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells or tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of an ovarian carcinoma protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches,

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Futura Publishing Co. (Mt. Kisco, NY; 1994). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

Any polynucleotide may be further modified to increase stability in vivo. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also

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be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

Ovarian Carcinoma Polypeptides

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof, as described herein. As noted above, certain ovarian carcinoma proteins are ovarian carcinoma antigens that are expressed by ovarian tumor cells and react detectably within an immunoassay (such as an ELISA) with antisera generated against serum from an immunodeficient animal implanted with an ovarian tumor. Other ovarian carcinoma proteins are encoded by ovarian carcinoma polynucleotides recited herein. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but

need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of an antigen that is recognized (i.e., specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of an ovarian carcinoma protein or a variant thereof. Preferred immunogenic portions are encoded by cDNA molecules isolated as described herein. Further immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with ovarian carcinoma protein-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "ovarian carcinoma protein-

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specific" if they specifically bind to an ovarian carcinoma protein (i.e., they react with the ovarian carcinoma protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera, antibodies and T cells may be prepared as described herein, and using well known techniques. An immunogenic portion of a native ovarian carcinoma protein is a portion that reacts with such antisera, antibodies and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length protein. Such screens may generally be 10 performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, 125 I-labeled Protein A.

As noted above, a composition may comprise a variant of a native ovarian carcinoma protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native ovarian carcinoma protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with ovarian carcinoma protein-specific antisera may be enhanced or unchanged, relative to the native ovarian carcinoma protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native ovarian carcinoma protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with ovarian carcinoma protein-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

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Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity to the native polypeptide. Preferably, a variant contains conservative substitutions. "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells

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include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises one polypeptide as described herein and a known tumor antigen, such as an ovarian carcinoma protein or a variant of such a protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused

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protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide . 10 folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding . Similarly, stop codons required to end translation and the first polypeptides. transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

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Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen present cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

Binding Agents

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The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to an ovarian carcinoma protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to an ovarian carcinoma protein if it reacts at a detectable level (within, for example, an ELISA) with an ovarian carcinoma protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a "complex" is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10³ L/mol. The binding constant maybe determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as ovarian cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a ovarian carcinoma antigen will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological

samples (e.g., blood, sera, leukophoresis, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the

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desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ⁹⁰Y, ¹²³I, ¹²⁵I, ¹³¹I, ¹⁸⁶Re, ¹⁸⁸Re, ²¹¹At, and ²¹²Bi. Preferred drugs include

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methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of

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derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

Also provided herein are anti-idiotypic antibodies that mimic an immunogenic portion of an ovarian carcinoma protein. Such antibodies may be raised against an antibody, or antigen-binding fragment thereof, that specifically binds to an



immunogenic portion of an ovarian carcinoma protein, using well known techniques. Anti-idiotypic antibodies that mimic an immunogenic portion of an ovarian carcinoma protein are those antibodies that bind to an antibody, or antigen-binding fragment thereof, that specifically binds to an immunogenic portion of an ovarian carcinoma protein, as described herein.

T Cells

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Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for an ovarian carcinoma protein. Such cells may generally be prepared in vitro or ex vivo, using standard procedures. For example, T cells may be present within 10 (or isolated from) bone marrow, peripheral blood or a fraction of bone marrow or peripheral blood of a mammal, such as a patient, using a commercially available cell separation system, such as the CEPRATE™ system, available from CellPro Inc., Bothell WA (see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human animals, cell lines or cultures.

T cells may be stimulated with an ovarian carcinoma polypeptide, polynucleotide encoding an ovarian carcinoma polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, an ovarian carcinoma polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for an ovarian carcinoma polypeptide if the T cells kill target cells coated with an ovarian carcinoma polypeptide or expressing a gene encoding such a polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be

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accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with an ovarian carcinoma polypeptide (200 ng/ml - 100 μ g/ml, preferably 100 ng/ml - 25 μ g/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells and/or contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-y) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998). T cells that have been activated in response to an ovarian carcinoma polypeptide, polynucleotide or ovarian carcinoma polypeptide-expressing APC may be CD4+ and/or CD8+. Ovarian carcinoma polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient or a related or unrelated donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to an ovarian carcinoma polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to an ovarian carcinoma polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize an ovarian carcinoma polypeptide. Alternatively, one or more T cells that proliferate in the presence of an ovarian carcinoma polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution. Following expansion, the cells may be administered back to the patient as described, for example, by Chang et al., *Crit. Rev. Oncol. Hematol. 22*:213, 1996.

Pharmaceutical Compositions and Vaccines

Within certain aspects, polypeptides, polynucleotides, binding agents 30 and/or immune system cells as described herein may be incorporated into

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pharmaceutical compositions or vaccines. Pharmaceutical compositions comprise one or more such compounds or cells and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds or cells and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the compound is incorporated; see e.g., Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., PNAS 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., PNAS 91:215-219, 1994; Kass-Eisler et al.,

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PNAS 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune

responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI), Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ), alum, biodegradable microspheres, monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). Also preferred is AS-2 (SmithKline Beecham). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO

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96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (i.e., a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects per se and/or to be immunologically compatible with the receiver (i.e., matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to

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be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (see Timmerman and Levy, Ann. Rev. Med. 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate in situ, with marked cytoplasmic processes (dendrites) visible in vitro) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells in vivo or ex vivo, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (see Zitvogel et al., Nature Med. 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fc γ receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80 and CD86).

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APCs may generally be transfected with a polynucleotide encoding a ovarian carcinoma antigen (or portion or other variant thereof) such that the antigen, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Cancer Therapy

In further aspects of the present invention, the compositions described

herein may be used for immunotherapy of cancer, such as ovarian cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Within certain preferred embodiments, a patient is afflicted with ovarian cancer. Such cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

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Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immuno response-modifying agents (such as tumor vaccines, bacterial adjuvants and/or cytokines).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigenpresenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4.918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system.

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Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term in vivo. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into stem cells taken from a patient and clonally propagated in vitro for autologous transplant back into the same patient.

Routes and frequency of administration, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injectión (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration), orally or in the bed of a resected tumor. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level.. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical

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outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to an ovarian carcinoma antigen generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

Screens for Identifying Secreted Ovarian Carcinoma Antigens

The present invention provides methods for identifying secreted tumor antigens. Within such methods, tumors are implanted into immunodeficient animals such as SCID mice and maintained for a time sufficient to permit secretion of tumor antigens into serum. In general, tumors may be implanted subcutaneously or within the gonadal fat pad of an immunodeficient animal and maintained for 1-9 months, preferably 1-4 months. Implantation may generally be performed as described in WO 97/18300. The serum containing secreted antigens is then used to prepare antisera in immunocompetent mice, using standard techniques and as described herein. Briefly, 50-100 µL of sera (pooled from three sets of immunodeficient mice, each set bearing a different SCID-derived human ovarian tumor) may be mixed 1:1 (vol:vol) with an appropriate adjuvant, such as RIBI-MPL or MPL + TDM (Sigma Chemical Co., St. Louis, MO) and injected intraperitoneally into syngeneic immunocompetent animals at monthly intervals for a total of 5 months. Antisera from animals immunized in such a manner may be obtained by drawing blood after the third, fourth and fifth immunizations. The resulting antiserum is generally pre-cleared of E. coli and phage antigens and used (generally following dilution, such as 1:200) in a serological expression screen.

The library is typically an expression library containing cDNAs from one or more tumors of the type that was implanted into SCID mice. This expression library may be prepared in any suitable vector, such as λ -screen (Novagen). cDNAs that encode a polypeptide that reacts with the antiserum may be identified using standard techniques, and sequenced. Such cDNA molecules may be further characterized to

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evaluate expression in tumor and normal tissue, and to evaluate antigen secretion in patients.

The methods provided herein have advantages over other methods for tumor antigen discovery. In particular, all antigens identified by such methods should be secreted or released through necrosis of the tumor cells. Such antigens may be present on the surface of tumor cells for an amount of time sufficient to permit targeting and killing by the immune system, following vaccination.

Methods for Detecting Cancer

In general, a cancer may be detected in a patient based on the presence of one or more ovarian carcinoma proteins and/or polynucleotides encoding such proteins in a biological sample (such as blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as ovarian cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of protein that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, an ovarian carcinoma-associated sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding

agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length ovarian carcinoma proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

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Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20TM (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (i.e., incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with ovarian cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over

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a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20TM. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibodypolypeptide complex for an amount of time sufficient to detect the bound polypeptide.

An appropriate amount of time may generally be determined by assaying the level of
binding that occurs over a period of time. Unbound detection reagent is then removed
and bound detection reagent is detected using the reporter group. The method employed
for detecting the reporter group depends upon the nature of the reporter group. For
radioactive groups, scintillation counting or autoradiographic methods are generally
appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups
and fluorescent groups. Biotin may be detected using avidin, coupled to a different
reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme
reporter groups may generally be detected by the addition of substrate (generally for a
specific period of time), followed by spectroscopic or other analysis of the reaction
products.

To determine the presence or absence of a cancer, such as ovarian cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity)

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that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

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Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use ovarian carcinoma polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such ovarian carcinoma protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with an ovarian carcinoma protein in a biological sample. Within certain methods, a biological sample comprising CD4+ and/or CD8+ T cells isolated from a patient is incubated with an ovarian carcinoma protein, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with an ovarian carcinoma protein (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of ovarian carcinoma protein to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding an ovarian carcinoma protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of an ovarian carcinoma protein cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the ovarian carcinoma protein. The amplified cDNA is then separated and detected using techniques well

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known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding an ovarian carcinoma protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding an ovarian carcinoma protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably. oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous 15 nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence provided herein. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample such as a biopsy tissue and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

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In another embodiment, ovarian carcinoma proteins and polynucleotides encoding such proteins may be used as markers for monitoring the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Certain in vivo diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple ovarian carcinoma protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

Diagnostic Kits

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to an ovarian carcinoma protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain



a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding an ovarian carcinoma protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding an ovarian carcinoma protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding an ovarian carcinoma protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

EXAMPLE 1

IDENTIFICATION OF REPRESENTATIVE OVARIAN CARCINOMA PROTEIN CDNAS

This Example illustrates the identification of cDNA molecules encoding ovarian carcinoma proteins.

Anti-SCID mouse sera (generated against sera from SCID mice carrying late passage ovarian carcinoma) was pre-cleared of E. coli and phage antigens and used at a 1:200 dilution in a serological expression screen. The library screened was made from a SCID-derived human ovarian tumor (OV9334) using a directional RH oligo(dT) priming cDNA library construction kit and the λScreen vector (Novagen). A bacteriophage lambda screen was employed. Approximately 400,000 pfu of the amplified OV9334 library were screened.

196 positive clones were isolated. Certain sequences that appear to be novel are provided in Figures 1A-1S and SEQ ID NO:1 to 71. Three complete insert sequences are shown in Figures 2A-2C (SEQ ID NO:72 to 74). Other clones having known sequences are presented in Figures 15A-15EEE (SEQ ID NO:82 to 310). Database searches identified the following sequences that were substantially identical to the sequences presented in Figures 15A-15EEE.

These clones were further characterized using microarray technology to

determine mRNA expression levels in a variety of tumor and normal tissues. Such
analyses were performed using a Synteni (Palo Alto, CA) microarray, according to the
manufacturer's instructions. PCR amplification products were arrayed on slides, with
each product occupying a unique location in the array. mRNA was extracted from the
tissue sample to be tested, reverse transcribed and fluorescent-labeled cDNA probes
were generated. The microarrays were probed with the labeled cDNA probes and the
slides were scanned to measure fluorescence intensity. Data was analyzed using
Synteni's provided GEMtools software. The results for one clone (13695, also referred
to as O8E) are shown in Figure 3.

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EXAMPLE 2

IDENTIFICATION OF OVARIAN CARCINOMA CDNAS USING MICROARRAY TECHNOLOGY

This Example illustrates the identification of ovarian carcinoma polynucleotides by PCR subtraction and microarray analysis. Microarrays of cDNAs were analyzed for ovarian tumor-specific expression using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997).

A PCR subtraction was performed using a tester comprising cDNA of four ovarian tumors (three of which were metastatic tumors) and a driver of cDNA form five normal tissues (adrenal gland, lung, pancreas, spleen and brain). cDNA fragments recovered from this subtraction were subjected to DNA microarray analysis where the fragments were PCR amplified, adhered to chips and hybridized with fluorescently labeled probes derived from mRNAs of human ovarian tumors and a variety of normal human tissues. In this analysis, the slides were scanned and the fluorescence intensity was measured, and the data were analyzed using Synteni's GEMtools software. In general, sequences showing at least a 5-fold increase in expression in tumor cells (relative to normal cells) were considered ovarian tumor antigens. The fluorescent results were analyzed and clones that displayed increased expression in ovarian tumors were further characterized by DNA sequencing and database searches to determine the novelty of the sequences.

Using such assays, an ovarian tumor antigen was identified that is a splice fusion between the human T-cell leukemia virus type I oncoprotein TAX (see Jin et al., Cell 93:81-91, 1998) and an extracellular matrix protein called osteonectin. A splice junction sequence exists at the fusion point. The sequence of this clone is presented in Figure 4 and SEQ ID NO:75. Osteonectin, unspliced and unaltered, was also identified from such assays independently.

Further clones identified by this method are referred to herein as 3f, 6b, 8e, 8h, 12c and 12h. Sequences of these clones are shown in Figures 5 to 9 and SEQ ID NO:76 to 81. Microarray analyses were performed as described above, and are presented in Figures 10 to 14. A full length sequence encompassing clones 3f, 6b, 8e



and 12h was obtained by screening an ovarian tumor (SCID-derived) cDNA library. This 2996 base pair sequence (designated O772P) is presented in SEQ ID NO:311, and the encoded 914 amino acid protein sequence is shown in SEQ ID NO:312. PSORT analysis indicates a Type 1a transmembrane protein localized to the plasma membrane.

In addition to certain of the sequences described above, this screen identified the following sequences which are described in detail in Table 1:

Table 1

Sequence	Comments
OV4vG11 (SEQ ID NO:313)	human clone 1119D9 on chromosome 20p12
OV4vB11 (SEQ ID NO:314)	human UWGC:y14c094 from chromosome 6p21
OV4vD9 (SEQ ID NO:315)	human clone 1049G16 chromosome 20q12-13.2
OV4vD5 (SEQ ID NO:316)	human KIAA0014 gene
OV4vC2 (SEQ ID NO:317)	human KIAA0084 gene
OV4vF3 (SEQ ID NO:318)	human chromosome 19 cosmid R31167
OV4VC1 (SEQ ID NO:319)	novel
OV4vH3 (SEQ ID NO:320)	novel
OV4vD2 (SEQ ID NO:321)	novel
O815P (SEQ ID NO:322)	novel
OV4vC12 (SEQ ID NO:323)	novel
OV4vA4 (SEQ ID NO:324)	novel
OV4vA3 (SEQ ID NO:325)	novel
OV4v2A5 (SEQ ID NO:326)	novel
O819P (SEQ ID NO:327)	novel
O818P (SEQ ID NO:328)	novel
O817P (SEQ ID NO:329)	novel
O816P (SEQ ID NO:330)	novel
Ov4vC5 (SEQ ID NO:331)	novel
21721 (SEQ ID NO:332)	human lumican
21719 (SEQ ID NO:333)	human retinoic acid-binding protein II
21717 (SEQ ID NO:334)	human26S proteasome ATPase subunit
21654 (SEQ ID NO:335)	human copine I
21627 (SEQ ID NO:336)	human neuron specific gamma-2 enolase



Sequence	Comments	
21623 (SEQ ID NO:337)	human geranylgeranyl transferase II	
21621 (SEQ ID NO:338)	human cyclin-dependent protein kinase	
21616 (SEQ ID NO:339)	human prepro-megakaryocyte potentiating factor	
21612 (SEQ ID NO:340)	human UPH1	
21558 (SEQ ID NO:341)	human RalGDS-like 2 (RGL2)	
21555 (SEQ ID NO:342)	human autoantigen P542	
21548 (SEQ ID NO:343)	human actin-related protein (ARP2)	
21462 (SEQ ID NO:344)	human huntingtin interacting protein	
21441 (SEQ ID NO:345)	human 90K product (tumor associated antigen)	
21439 (SEQ ID NO:346)	human guanine nucleotide regulator protein (tim1)	
21438 (SEQ ID NO:347)	human Ku autoimmune (p70/p80) antigen	
21237 (SEQ ID NO:348)	human S-laminin	
21436 (SEQ ID NO:349)	human ribophorin I	
21435 (SEQ ID NO:350)	human cytoplasmic chaperonin hTRiC5	
21425 (SEQ ID NO:351)	humanEMX2	
21423 (SEQ ID NO:352)	human p87/p89 gene	
21419 (SEQ ID NO:353)	human HPBRII-7	
21252 (SEQ ID NO:354)	human T1-227H	
21251 (SEQ ID NO:355)	human cullin I	
21247 (SEQ ID NO:356)	kunitz type protease inhibitor (KOP)	
21244-1 (SEQ ID NO:357)	human protein tyrosine phosphatase receptor F (PTPRF)	
21718 (SEQ ID NO:358)	human LTR repeat	
OV2-90 (SEQ ID NO:359)	novel	
Human zinc finger (SEQ ID NO):360)	
Human polyA binding protein (SEQ ID NO:361)		
Human pleitrophin (SEQ ID NO:362)		
Human PAC clone 278C19 (SEQ ID NO:363)		
Human LLRep3 (SEQ ID NO:364)		
Human Kunitz type protease inhib (SEQ ID NO:365)		
Human KIAA0106 gene (SEQ ID NO:366)		
Human keratin (SEQ ID NO:367)		
Human HIV-1TAR (SEQ ID NO:368)		
Human glia derived nexin (SEQ ID NO:369)		



Sequence	Comments	
Human fibronectin (SEQ ID NO:370)		
Human ECMproBM40 (SEQ ID NO:371)		
Human collagen (SEQ ID NO:372)		
Human alpha enolase (SEQ ID NO:373)		
Human aldolase (SEQ ID NO:374)		
Human transf growth factor BIG H3 (SEQ ID NO:375)		
Human SPARC osteonectin (SEQ ID NO:376)		
Human SLP1 leucocyte protease (SEQ ID NO:377)		
Human mitochondrial ATP synth (SEQ ID NO:378)		
Human DNA seq clone 461P17 (SEQ ID NO:379)		
Human dbpB pro Y box (SEQ ID NO:380)		
Human 40 kDa keratin (SEQ ID NO:381)		
Human arginosuccinate synth (SEQ ID NO:382)		
Human acidic ribosomal phosphoprotein (SEQ ID NO:383)		
Human colon carcinoma laminin binding pro (SEQ ID NO:384)		

This screen further identified multiple forms of the clone O772P, referred to herein as 21013, 21003 and 21008. PSORT analysis indicates that 21003 (SEQ ID NO:386; translated as SEQ ID NO:389) and 21008 (SEQ ID NO:387; translated as SEQ ID NO:390) represent Type 1a transmembrane protein forms of O772P. 21013 (SEQ ID NO:385; translated as SEQ ID NO:388) appears to be a truncated form of the protein and is predicted by PSORT analysis to be a secreted protein.

Additional sequence analysis resulted in a full length clone for O8E (2627 bp, which agrees with the message size observed by Northern analysis; SEQ ID NO:391). This nucleotide sequence was obtained as follows: the original O8E sequence (OrigO8Econs) was found to overlap by 33 nucleotides with a sequence from an EST clone (IMAGE#1987589). This clone provided 1042 additional nucleotides upstream of the original O8E sequence. The link between the EST and O8E was confirmed by sequencing multiple PCR fragments generated from an ovary primary tumor library using primers to the unique EST and the O8E sequence (ESTxO8EPCR). Full length status was further indicated when anchored PCR from the ovary tumor library gave

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several clones (AnchoredPCR cons) that all terminated upstream of the putative start methionine, but failed to yield any additional sequence information. Figure 16 presents a diagram that illustrates the location of each partial sequence within the full length O8E sequence.

Two protein sequences may be translated from the full length O8E. For "a" (SEQ ID NO:393) begins with a putative start methionine. A second form "b" (SEQ ID NO:392) includes 27 additional upstream residues to the 5' end of the nucleotide sequence.

EXAMPLE 3

This example discloses the identification and characterization of antibody epitopes recognized by the O8E polyclonal anti-sera.

Rabbit anti-sera was raised against E. coli derived O8E recombinant protein and tested for antibody epitope recognition against 20 or 21 mer peptides that correspond to the O8E amino acid sequence. Peptides spanning amino acid regions 31 to 65, 76 to 110, 136 to 200 and 226 to 245 of the full length O8E protein were recognized by an acid eluted peak and/or a salt eluted peak from affinity purified anti-O8E sera. Thus, the corresponding amino acid sequences of the above peptides constitute the antibody epitopes recognized by affinity purified anti-O8E antibodies.

ELISA analysis of anti-08E rabbit sera is shown in Figure 23, and ELISA 20 analysis of affinity purified rabbit anti-08E polyclonal antibody is shown in Figure 24.

For epitope mapping, 20 or 21 mer peptides corresponding to the O8E protein were synthesized. For antibody affinity purification, rabbit anti-O8E sera was run over an O8E-sepharose column, then antibody was eluted with a salt buffer containing 0.5 M NaCl and 20 mM PO₄, followed by an acid elution step using 0.2 M Glycine, pH 2.3. Purified antibody was neutralized by the addition of 1M Tris, pH 8 and buffer exchanged into phosphate buffered saline (PBS). For enzyme linked immunosorbant assay (ELISA) analysis, O8E peptides and O8E recombinant protein were coated onto 96 well flat bottom plates at 2 μg/ml for 2 hours at room temperature (RT). Plates were then washed 5 times with PBS + 0.1 % Tween 20 and blocked with PBS + 1 % bovine serum albumin (BSA) for 1 hour. Affinity purified anti-O8E antibody, either an acid or salt eluted fraction, was then added to the wells at 1 μg/ml

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and incubated at RT for 1 hr. Plates were again washed, followed by the addition of donkey anti-rabbit-Ig-horseradish peroxidase (HRP) antibody for 1 hour at RT. Plates were washed, then developed by the addition of the chromagenic substrate 3, 3', 5, 5'-tetramethylbenzidine (TMB) (described by Bos et al., J. of Immunoassay 2:187-204 (1981); available from Sigma (St. Louis, MO)). The reaction was incubated 15 minutes at RT and then stopped by the addition of 1 N H₂SO₄. Plates were read at an optical density of 450 (OD450) in an automated plate reader. The sequences of peptides corresponding to the OE8 antibody epitopes are disclosed herein as SEQ ID NO: 394-415. Antibody epitopes recognized by the O8E polyclonal anti-sera are disclosed herein in Figure 17.

EXAMPLE 4

This example discloses IHC analysis of O8E expression in ovarian cancer tissue samples.

For immunohistochemistry studies, paraffin-embedded formalin fixed ovarian cancer tissue was sliced into 8 micron sections. Steam heat induced epitope retrieval (SHIER) in 0.1 M sodium citrate buffer (pH 6.0) was used for optimal staining conditions. Sections were incubated with 10% serum/PBS for 5 minutes. Primary antibody (anti-O8E rabbit affinity purified polyclonal antibody) was added to each section for 25 min followed by a 25 min incubation with an anti-rabbit biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 min incubations with hydrogen peroxidase. The avidin biotin complex/horse radish peroxidase system was used along with DAB chromogen to visualize antigen expression. Slides were counterstained with hematoxylin. One (papillary serous carcinoma) of six ovarian cancer tissue sections displayed O8E immunoreactivity. Upon optimization of the staining conditions, 4/5 ovarian cancer samples stained positive using the O8E polyclonal antibody. O8E expression was localized to the plasma membrane.

Six ovarian cancer tissues were analyzed with the anti-O8E rabbit polyclonal antibody. One (papillary serous carcinoma) of six ovarian cancer tissue samples stained positive for O8E expression. O8E expression was localized to the surface membrane.

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EXAMPLE 5

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This example discloses O8E peptides that are predicted to bind HLA-A2 and to be immunogenic for CD8 T cell responses in humans.

Potential HLA-A2 binding peptides of O8E were predicted by using the full-length open-reading frame (ORF) from O8E and running it through "Episeek," a program used to predict MHC binding peptides. The program used is based on the algorithm published by Parker, K.C. et al., J. Immunol. 152(1):163-175 (1994) (incorporated by reference herein in its entirety). 10-mer and 9-mer peptides predicted to bind HLA-0201 are disclosed herein as SEQ ID NO: 416-435 and SEQ ID NO: 436-455, respectively.

EXAMPLE 6

This example discloses O8E cell surface expression measured by fluoresence activated cell sorting.

For FACS analysis, cells were washed with ice cold staining buffer (PBS/1% BSA/azide). Next, the cells were incubated for 30 minutes on ice with 10 micrograms/ml of affinity purified rabbit anti-B305D polyclonal antibody. The cells were washed 3 times with staining buffer and then incubated with a 1:100 dilution of a goat anti-rabbit Ig (H+L)-FITC reagent (Southern Biotechnology) for 30 minutes on ice. Following 3 washes, the cells were resuspended in staining buffer containing prodium iodide, a vital stain that allows for identification of permeable cells, and analyzed by FACS. O8E surface expression was confirmed on SKBR3 breast cancer cells and HEK293 cells that stably overexpress the cDNA for O8E. Neither MB415 cells nor HEK293 cells stably transfected with a control irrelevant plasmid DNA showed surface expression of O8E (Figures 18 and 19).

25 EXAMPLE 7

This example further evaluates the expression and surface localization of OSE.

For expression and purification of antigen used for immunization, O8E expressed in an E. coli recombinant expression system was grown overnight in LB 30 Broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning,



10 ml of the overnight culture was added to 500 ml of 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nanometers) of the culture reached 0.4-0.6 the cells were induced with IPTG (1 mM). 4 hours after induction with IPTG the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty milliliters of lysis buffer was added to the cell pellets and vortexed. To break open the E. coli cells, this mixture was then run through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For protein that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0 , 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A 20 SDS-PAGE gel was run to determine which fractions to pool for further purification. As a final purification step, a strong anion exchange resin such as Hi-Prep Q (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off of the column with an increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. This material was then evaluated for acceptable purity as determined by SDS-PAGE or HPLC, concentration as determined by Lowry assay or Amino Acid Analysis, identity as determined by amino terminal protein sequence, and endotoxin level as determined by the Limulus (LAL) assay. The

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proteins were then vialed after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

For generation of polyclonal anti-sera, 400 micrograms of each prostate antigen was combined with 100 micrograms of muramyldipeptide (MDP). Equal volume of Incomplete Freund's Adjuvant (IFA) was added and then mixed. Every four weeks animals were boosted with 100 micrograms of antigen mixed with an equal volume of IFA. Seven days following each boost the animal was bled. Sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

For characterization of polyclonal antisera, 96 well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) at 4°C for 20 hrs. 250 microliters of BSA blocking buffer was added to the wells and incubated at RT for 2 hrs. Plates were washed 6 times with PBS/0.01% tween. Anti-O8E rabbit sera or affinity purified anti-O8e antibody was diluted in PBS. Fifty microliters of diluted antibody was added to each well and incubated at RT for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at RT for 30 min. Plates were washed as described above and 100 microliters of TMB microwell Peroxidase Substrate was added to each well. Following a 15 minute incubation in the dark at room temperature the colorimetric reaction was stopped with 100 microliters of 1N H2SO4 and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity to the O8E antigen.

For recombinant expression in mammalian HEK293 cells, full length O8E cDNA was subcloned into the mammalian expression vectors pcDNA3.1+ and pCEP4 (Invitrogen) which were modified to contain His and FLAG epitope tags, respectively. These constructs were transfected into HEK293 cells (ATCC) using Fugene 6 reagent (Roche). Briefly, HEK293 cells were plated at a density of 100,000 cells/ml in DMEM (Gibco) containing 10% FBS (Hyclone) and grown overnight. The following day, 2 ul of Fugene6 was added to 100 ul of DMEM containing no FBS and incubated for 15 minutes at room temperature. The Fugene6/DMEM mixture was then added to 1ug of O8E/pCEP4 or O8E/pcDNA3.1 plasmid DNA and incubated for 15 minutes at room temperature. The Fugene/DNA mix was then added to the HEK293



cells and incubated for 48-72 hrs at 37oC with 7% CO2. Cells were rinsed with PBS then collected and pelleted by centrifugation. For Western blot analysis, whole cell lysates were generated by incubating the cells in Triton-X100 containing lysis buffer for 30 minutes on ice. Lysates were then cleared by centrifugation at 10,000rpm for 5 minutes at 4 C. Samples were diluted with SDS-PAGE loading buffer containing beta-mercaptoethanol, then boiled for 10 minutes prior to loading the SDS-PAGE gel. Protein was transferred to nitrocellulose and probed using anti-O8E rabbit polyclonal sera #2333L at a dilution of 1:750. The blot was revealed with a goat anti-rabbit Ig coupled to HRP followed by incubation in ECL substrate.

For FACS analysis, cells were washed further with ice cold staining buffer (PBS+1%BSA+Azide). Next, the cells were incubated for 30 minutes on ice with 10ug/ml of Protein A purified anti-O8E polyclonal sera. The cells were washed 3 times with staining buffer and then incubated with a 1:100 dilution of a goat anti-rabbit Ig(H+L)-FITC reagent (Southern Biotechnology) for 30 minutes on ice. Following 3 washes, the cells were resuspended in staining buffer containing Propidium Iodide (PI), a vital stain that allows for the identification of permeable cells, and analyzed by FACS.

From these experiments, the results of which are illustrated in Figures 20-21, O8E expression was detected on the surface of transfected HEK293 cells and SKBR3 cells by FACS analysis using rabbit anti-O8E sera. Expression was also detected in transfected HEK293 cell lysates by Western blot analysis (Figure 22).

EXAMPLE 8

GENERATION AND CHARACTERIZATION OF ANTI-O8E MABS.

Mouse monoclonal antibodies were raised against E. coli derived O8E proteins as follows. A/J mice were immunized intraperitoneally (IP) with Complete Freund's Adjuvant (CFA) containing 50 µg recombinant O8E, followed by a subsequent IP boost with Incomplete Freund's Adjuvant (IFA) containing 10µg recombinant O8E protein. Three days prior to removal of the spleens, the mice were immunized intravenously with approximately 50µg of soluble O8E recombinant protein. The spleen of a mouse with a positive titer to O8E was removed, and a single-cell suspension made and used for fusion to SP2/0 myeloma cells to generate B cell

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hybridomas. The supernatants from the hybrid clones were tested by ELISA for specificity to recombinant O8E, and epitope mapped using peptides that spanned the entire O8E sequence. The mAbs were also tested by flow cytometry for their ability to detect O8E on the surface of cells stably transfected with O8E and on the surface of a breast tumor cell line.

For ELISA analysis, 96 well plates were coated with either recombinant O8E protein or overlapping 20-mer peptides spanning the entire O8E molecule at a concentration of either 1-2µg/ml or 10µg/ml, respectively. After coating, the plates were washed 5 times with washing buffer (PBS + 0.1% Tween-20) and blocked with PBS containing 0.5% BSA, 0.4% Tween-20. Hybrid supernatants or purified mAbs were then added and the plates incubated for 60 minutes at room temperature. The plates were washed 5 times with washing buffer and the secondary antibody, donkeyanti mouse Ig linked to horseradish peroxidase (HRP)(Jackson ImmunoResearch), was added for 60 minutes. The plates were again washed 5 times in washing buffer, followed by the addition of the peroxidase substrate. Of the hybridoma clones generated, 15 secreted mAbs that recognized the entire O8E protein. Epitope mapping revealed that of these 15 clones, 14 secreted mAbs that recognized the O8E amino acid residues 61-80 and one clone secreted a mAb that recognized amino acid residues 151-170.

For flow cytometric analysis, HEK293 cells which had been stably transfected with O8E and SKBR3 cells which express O8E mRNA, were harvested and washed in flow staining buffer (PBS+1%BSA+Azide). The cells were incubated with the supernatant from the mAb hybrids for 30 minutes on ice followed by 3 washes with staining buffer. The cells were incubated with goat-anti mouse Ig-FITC for 30 minutes on ice, followed by three washes with staining buffer before being resuspended in wash buffer containing propidium iodide. Flow cytometric analysis revealed that 15/15 mAbs were able to detect O8E protein expressed on the surface of O8E-transfected HEK293 cells. 6/6 mAbs tested on SKBR3 cells were able to recognize surface expressed O8E.

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EXAMPLE 9

EXTENDED DNA AND PROTEIN SEQUENCE ANALYSIS OF SEQUENCE O772P

A full-length sequence encompassing clones 3f, 6b, 8e, and 12 was obtained by screening an ovarian tumor (SCID-derived) cDNA library described in detail in Example 2. This 2996 base pair sequence, designated O772P, is presented in SEQ ID NO: 311, and the encoded 914 amino acid protein sequence is shown in SEQ ID NO: 312. The DNA sequence O772P was searched against public databases including Genbank and showed a significant hit to Genbank Accession number AK024365 (SEQ ID NO: 457). This Genbank sequence was found to be 3557 base pairs in length and encodes a protein 1156 amino acids in length (SEQ ID NO: 459). A truncated version of this sequence, residues 25-3471, in which residue 25 corresponds to the first ATG initiation codon in the Genbank sequence, (SEQ ID NO: 456), encodes a protein that is 1148 amino acids in length (SEQ ID NO: 458). The published DNA sequence (SEQ ID NO: 457) differs from O772P in that it has a 5 base pair insertion corresponding to bases 958-962 of SEQ ID NO: 457. This insertion results in a frame shift such that SEQ ID NO: 457 encodes an additional N-terminal protein sequence relative to O772P (SEQ ID NO: 312). In addition, O772P encodes a unique N-terminal portion contained in residues 1-79 (SEQ ID NO: 460). The N-terminal portion of SEQ ID NO: 456, residues 1-313, also contains unique sequence and is listed as SEQ ID NO: 461.

EXAMPLE 10

THE GENERATION OF POLYCLONAL ANTIBODIES FOR IMMUNOHISTOCHEMISTRY AND FLOW CYTOMETRIC ANALYSIS OF THE CELL ASSOCIATED EXPRESSION PATTERN OF MOLECULE O772P

The O772P molecule was identified in Examples 2 and 9 of this application. To evaluate the subcellular localization and specificity of antigen expression in various tissues, polyclonal antibodies were generated against O772P. To produce these antibodies, O772P-1 (amino acids 44-772 of SEQ ID NO:312) and O772P-2 (477-914 of SEQ ID NO:312) were expressed in an E. coli recombinant expression system and grown overnight at 37°C in LB Broth. The following day, 10ml

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of the overnight culture was added to 500ml of 2xYT containing the appropriate antibiotics. When the optical density of the cultures (560 nanometers) reached 0.4-0.6 the cells were induced with IPTG. Following induction, the cells were harvested, washed, lysed and run through a French Press at a pressure of 16000 psi. The cells were then centrifuged and the pellet checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localize to the cell pellet, the pellet was resuspended in 10mM Tris, pH 8.0, 1% CHAPS and the inclusion body pellet washed and centrifuged. The washed inclusion body was solubilized with either 8M urea or 6M guanidine HCL containing 10mM Tris, pH 8.0, plus 10mM imidazole. The solubilized protein was then added to 5ml of nickel-chelate resin (Qiagen) and incubated for 45 minutes at room temperature.

Following the incubation, the resin and protein mixture was poured through a column and the flow through collected. The column was washed with 10-20 column volumes of buffer and the antigen eluted using 8M urea, 10mM Tris, pH 8.0, and 300 mM imidazole and collected in 3ml fractions. SDS-PAGE was run to determine which fractions to pool for further purification. As a final purification step, a strong anion exchange resin was equilibrated with the appropriate buffer and the pooled fractions were loaded onto the column. Each antigen was eluted from the column with an increasing salt gradient. Fractions were collected and analyzed by a SDS-PAGE to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10mM Tris, pH 8.0, and the resulting protein was submitted for quality control for final release. The release criteria were: (a) purity as determined by SDS-PAGE or HPLC, (b) concentration as determined by Lowry assay or Amino Acid Analysis, (c) identity as determined by amino terminal protein, and (d) endotoxin levels as determined by the Limulus (LAL) assay. The proteins were then filtered through a 0.22μM filter and frozen until needed for immunizations.

To generate polyclonal antisera, 400μg of O772P-1 or O772P-2 was combined with 100μg of muramyldipeptide (MDP). The rabbits were immunized every 4 weeks with 100μg of antigen mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animals were bled and sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

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To characterize the antisera, 96 well plates were coated with antigen followed by blocking with BSA. Rabbit sera was diluted in PBS and added to each well. The plates were then washed, and goat anti-rabbit horseradish peroxidase (HRP). The plates were again washed and TMB microwell Peroxidase Substrate was added. Following this incubation, the colormetric reaction was stopped and the plates read immediately at 450nm. All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

Immunohistochemistry analysis of O772P expression was performed on paraffin-embedded formalin fixed tissue. O772P was found to be expressed in normal ovary and ovarian tumor, but not in normal heart, kidney, colon, lung or liver. Additionally, immunohistochemistry and flow cytometric analysis indicates that O772P is a plasma membrane-associated molecule. O772P contains 1 plasma transmembrane domain predicted to be encoded by amino acids 859-880. The N-terminus of O772P is extracellular and is encoded by amino acids 1-859, while the C-terminus is intracellular. Sequence analysis shows that there are 17 potential N-linked glycosylation sites.

EXAMPLE 11

O772P IS EXPRESSED ON THE SURFACE OF PRIMARY OVARIAN TUMOR CELLS

For recombinant expression in mammalian cells, the O772P-21008 (SEQ ID NO:387) and O772P full length cDNA (SEQ ID NO:311 encoding the protein of SEQ ID NO:312) were subcloned into mammalian expression vectors pBIB or pCEP4 respectively. These constructs were transfected into HEK293 cells using Fugene 6 (Roche). The HEK cells were then plated at a density of 100,000 cells/ml in DMEM containing fetal bovine serum (FBS) and grown overnight. The following day, 2µl of Fugene 6 was added to 100µl of DMEM, which contained no FBS, and incubated for 15 minutes at room temperature. The Fugene 6/DMEM mixture was then added to 1µg of O772P/pBIB or O772P/pCEP4 plasmid DNA and incubated for an additional 15 minutes at room temperature. The Fugene 6/DNA mix was then added to the HEK293 cells and incubated for 48-72 hours at 37°C with 7% CO₂. The cells were rinsed and pelleted by centrifugation.

For Western Blot analysis, whole cell lysates were generated by incubating the cells in lysis buffer followed by clarification by centrifugation. The samples were diluted and run on SDS-PAGE. The gel was then transferred to nitrocellulose and probed using purified anti-O772P-2 rabbit polyclonal antibody. The blot was revealed with a goat anti-rabbit Ig coupled to HRP followed by incubation in ECL substrate. Western Blot analysis revealed that O772P-21008 could be detected in HEK293 cells that had been transfected with O772P.

To determine the cell expression profile of O772P in cells, primary ovarian tumor cells were grown in SCID mice. The cells were retrieved from the mice and analyzed by flow cytometry. Briefly, cells washed in cold staining buffer containing PBS, 1% BSA, and Na Azide. The cells were incubated for 30 minutes with 10µg/ml of purified anti-O772P-1 and O772P-2 polyclonal sera. Following this incubation, the cells were washed three times in staining buffer and incubated with goat anti-rabbit Ig (H+L) conjugated to FITC (Southern Biotechnology). The cells were washed and resuspended in staining buffer containing Propidium Iodide (PI), a vital stain that identifies non-viable cells. The cells were then analyzed using Fluorescence Activated Cell Sorting (FACS). FACS analysis revealed that O772P was present on the cells surface. Surface expression of O772P on tumor cells allows for immune targeting by therapeutic antibodies.

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EXAMPLE 12

FUNCTIONAL CHARACTERIZATION OF ANTI-O8E MONOCLONAL ANTIBODIES

Mouse monoclonal antibodies (mAb) raised against E. coli derived O8E, as described in Example 8, were tested for their ability to promote O8E antigen internalization. Internalization of the antibody was determined using an in vitro cytotoxicity assay. Briefly, HEK293 and O8E/HEK transfected cells were plated into 96 well plates containing DME plus 10% heat-inactivated FBS in the presence of 50ng/well of purified anti-O8E or control antibodies. The isotype of the anti-O8E mAbs are as follows: 11A6-IgG1/kappa, 15C6-IgG2b/kappa, 18A8-IgG2b/kappa, and 14F1-IgG2a/kappa. W6/32 is a pan anti-human MHC class I mouse monoclonal antibody that serves as a positive control, and two irrelevant mAbs, Ir-Pharm and Ir-

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Crxa were included as negative controls. Following incubation with the O8E specific antibodies or the relevant controls antibodies, the mAb-zap, a goat anti-mouse Igsaporin conjugated secondary antibody (Advanced Targeting Systems) was added at a concentration of 100ng/ml to half of the wells, and the plates were incubated for 48 to 72 hours at 37°C in a 7% CO2 incubator. This assay takes advantage of the toxic nature of saporin, a ribozyme inactivating protein, which when internalized has a cytotoxic effect. Following incubation with the mAb-zap, internalization was quantitated by the addition of MTS reagent, followed by reading the OD490 of the plate on a microplate ELISA reader. Figure 25 depicts the results from these assays. The top panel represents HEK cells that have not been transfected with O8E and therefore O8E antibody should not bind and be internalized. Levels of proliferation were the same in all samples whether they were incubated with or without the mAb-zap, with the exception of the positive control Ab, W6/32. The lower panel represents cells that have been transfected with O8E and therefore should bind O8E specific antibodies. Antibodies from the hybridomas 11H6, 14F1, and 15C6, which recognize the amino acids 61-80 of O8E were able to promote internalization of the O8E surface protein as measured by decreased levels of proliferation due to the toxic nature of the mAb-zap (See Figure 25). The antibody generated by the hybridoma 18A8, which recognizes amino acids 151-170 of O8E, was unable to promote internalization as determined by normal levels of proliferation either in the absence or presence of the mAb-zap.

EXAMPLE 13

CHARACTERIZATION OF THE OVARIAN TUMOR ANTIGEN, O772P

The cDNA and protein sequences for multiple forms of the ovarian tumor antigen O772P have been described in the above (e.g., Examples 2 and 9). A Genbank search indicated that O772P has a high degree of similarity with FLJ14303 (Accession # AK024365; SEQ ID NO:457 and 463). Protein sequences corresponding to O772P and FLJ14303 are disclosed in SEQ ID NO:478 and 479, respectively. FLJ14303 was identical to the majority of O772P, with much of the 3'-end showing 100% homology. However, the 5'-end of FLJ14303 was found to extend further 5' than O772P. In addition, FLJ14303 contained a 5 bp insert (SEQ ID NO:457) resulting in a

frame shift of the amino-terminus protein sequence such that FLJ14303 utilizes a different starting methionine than O772P and therefore encodes a different protein. This insertion was present in the genomic sequence and seen in all EST clones that showed identity to this region, suggesting that FLJ14303 (SEQ ID NO:457) represents a splice variant of O772P, with an ORF that contains an extended and different amino-terminus. The additional 5'-nucleotide sequence included repeat sequences that were identified during the genomic mapping of O772P. The 5'-end of O772P and the corresponding region of FLJ14303 showed between 90-100% homology. Taken together, this suggests that O772P and FLJ14303 are different splice variants of the same gene, with different unique repeat sequences being spliced into the 5'-end of the gene.

The identification of an additional ten or more repeat sequences within the same region of chromosome 19, indicates that there may be many forms of O772P, each with a different 5'-end, due to differential splicing of different repeat sequences. Northern blot analysis of O772P demonstrated multiple O772P-hybridizing transcripts of different sizes, some in excess 10kb.

Upon further analysis, 13 additional O772P-related sequences were identified, the cDNA and amino acid sequences of which are described in Table 2.

Table 2

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SEQ ID NO:	Description	Transmembrane Domains
464 .	LS #1043400.1 (cDNA)	nd
465	LS #1043400.10 (cDNA)	0
466	LS #1043400.11 (cDNA)	2
467	LS #1043400.12 (cDNA)	2
468	LS #1043400.2 (cDNA)	nd
469	LS #1043400.3 (cDNA)	
470	LS #1043400.5 (cDNA)	nd
471	LS #1043400.8 (cDNA)	1
472	LS #1043400.9 (cDNA)	0

473	LS #1043400.6 (cDNA)	nd
474	LS #1043400.7 (cDNA)	nd
475	LS #1043400.4 (cDNA)	nd
476	LS #1397610.1 (cDNA)	0
477	1043400.10 Novel 5' (cDNA)	_
480	LS #1043400.9 (amino acid)	-
481	LS #1043400.8B (amino acid)	-
	Contains a transmembrane	·
	domain	
482	LS #1043400.8A (amino acid)	-
483	LS #1043400.12 (amino acid)	-
	Contains a transmembrane	
	domain	
484	LS #1043400.11B (amino acid)	-
	Contains a transmembrane	
	domain	
485	LS #1043400.11A (amino acid)	-
486	LS #1043400.10 (amino acid)	-
487	LS #1043400.1 (amino acid)	

nd=not determined

Initially it appeared that these sequences represented overlapping and/or discrete sequences of O772P splice forms that were capable of encoding polypeptides unique to the specific splice forms of O772P. However, nucleotide alignment of these sequences failed to identify any identical regions within the repeat elements. This indicates that the sequences may represent different specific regions of a single O772P gene, one that contains 16 or more repeat domains, all of which form a single linear transcript. The 5'-end of sequence LS #1043400.10 (Table 2; SEQ ID NO:465) is unique to both O772P and FLJ14303 and contains no repeat elements, indicating that this sequence may represent the 5'-end of O772P.

Previously, transmembrane prediction analysis had indicated that O772P contained between 1 and 3 transmembrane spanning domains. This was verified by the

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use of immunohistochemistry and flow cytometry, which demonstrated the existence of a plasma membrane-associated molecule representing O772P. However, immunohistochemistry also indicated the presence of secreted form(s) of O772P, possibly resulting from an alternative splice form of O772P or from a post-translational cleavage event. Analysis of several of the sequences presented in Table 2 showed that sequences 1043400B.12, 1043400.8B, and 1043400.11B all contained transmembrane regions, while 1043400.8A, 1043400.10, 1043400.1, 1043400.11A, and 1043400.9 were all lacking transmembrane sequences, suggesting that these proteins may be secreted.

Analysis indicates a part of O772P is expressed and/or retained on the plasma membrane, making O772P an attractive target for directing specific immunotherapies, e.g., therapeutic antibodies, against this protein. The predicted extracellular domain of O772P is disclosed in SEQ ID NO:489 and secretion of O772P is likely to occur as a result of a cleavage event within the sequence:

SLVEQVFLD<u>K</u>TLNASFHWLGSTYQLVDIHVTEMESSVYQP.

Proteolytic cleavage is most likely to occur at the Lysine (K) at position 10 of SEQ ID NO:489. The extracellular, transmembrane, and cytoplasmic regions of O772P are all disclosed in SEQ ID NO:488:

Extracellular:

SLVEQVFLDKTLNASFHWLGSTYQLVDIHVTEMESSVYQPTSSSS
TQHFYLNFTITNLPYSQDKAQPGTTNYQRNKRNIEDALNQLFRNSSIKSYFSDCQ
VSTFRSVPNRHHTGVDSLCNFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDR
SSVLVDGYFPNRNEPLTGNSDLPF

Transmembrane:

WAVILIGLAGLLGLITCLICGVLVTT

Cytoplasmic:

RRRKKEGEYNVQQQCPGYYQSHLDLEDLQ

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EXAMPLE 14

IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS OF O8E EXPRESSION IN OVARIAN CANCER AND NORMAL TISSUES

In order to determine which tissues express the ovarian cancer antigen O8E, IHC analysis was performed on a diverse range of tissue sections using both polyclonal and monoclonal antibodies specific for O8E. The generation of O8E specific polyclonal antibodies is described in detail in Example 8. The monoclonal antibodies used for staining were 11A6 and 14F1, both of which are specific for amino acids 61-80 of O8E and 18A8, which recognizes amino acids 151-170 of O8E (see Example 12 for details on generation).

To perform staining, tissue samples were fixed in formalin solution for 12-24 hours and embedded in paraffin before being sliced into 8 micron sections. Steam heat induced epitope retrieval (SHEIR) in 0.1M sodium citrate buffer (pH 6.0) was used for optimal staining conditions. Sections were incubated with 10% serum/PBS for 5 minutes. Primary antibody was then added to each section for 25 minutes followed by 25 minutes of incubation with either anti-rabbit or anti-mouse biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 minute incubations with hydrogen peroxidase. The avidin biotin complex/horse radish peroxidase (ABC/HRP) system was used along with DAB chromogen to visualize the antigen expression. Slides were counterstained with hematoxylin to visualize the cell nuclei.

Results using rabbit affinity purified polyclonal antibody to O8E (a.a. 29-283; for details on the generation of this Ab, see Example 3) are presented in Table 3. Results using the three monoclonal antibodies are presented in Table 4.

<u>Table 3</u>

Immunohistochemistry analysis of O8E using polyclonal antibodies

Tissue	O8E Expression	
Ovarian Cancer	Positive	
Breast Cancer	Positive	



Normal Ovary	Positive	
Normal Breast	Positive	
Blood Vessel	Positive	
Kidney	Negative	
Lung	Negative	
Colon	Negative	
Liver	Negative	
Heart	Negative	

<u>Table 4</u>
<u>Immunohistochemistry analysis of O8E using monoclonal antibodies</u>

Normal	11A6		18A8		14F1	
Tissue	Endothelia	Epithelial	Endothelial	Epithelial	Endothelial	Epithelial
	1	_				
Skin	2	2	0	0	1	1
Skin ·	1	1	0	0	1 .	1
Breast	0	1	n/a	n/a	1	1
Colon	0	0	0	0	0	0
Jejunum	0	0	0	0	0	0
Colon	0	0	0	0	0	0
Colon	0	0	0	0	0	0
Ovary	0	0	0	0	1	0 .
Colon	0	0	0	0	0	1
Liver	0	0	0	0	1	2
Skin	0	0	0	0	1	0
Duodenum	0	0	0	0	0	0
and Pancreas						
Appendix	0	0	0	0	0	0
Ileum	0	0	0	0	0	0

0=no staining, 1=light staining, 2=moderate staining, n/a=not available

EXAMPLE 15

EPITOPE MAPPING OF O772P POLYCLONAL ANTIBODIES

To perform epitope mapping of O772P, peptides were generated, the sequences of which were derived from the sequence of O772P. These peptides were 15 mers that overlapped by 5 amino acids and were generated via chemical synthesis on membrane supports. The peptides were covalently bound to Whatman 50 cellulose support by their C-terminus with the N-terminus unbound. In order to determine epitope specificity, the membranes were wet with 100% ethanol for 1 minute, and then blocked for 16 hours in TBS/Tween/Triton buffer (50mM Tris, 137 mM NaCl, 2.7 mM KCl, 0.5% BSA, 0.05% Tween 20, 0.05% Triton X-100, pH 7.5). The peptides were then probed with 2 O772P specific antibodies, O772P-1 (amino acids 44-772 of SEQ ID NO:312) and O772P-2 (477-914 of SEQ ID NO:312; see Example 10 for details of antibody generation), as well as irrelevant rabbit antibodies for controls. The antibodies were diluted to 1µg/ml and incubated with the membranes for 2 hours at room temperature. The membranes were then washed for 30 minutes in TBS/Tween/Triton buffer, prior to being incubated with a 1:10,000 dilution of HRP-conjugated anti-rabbit secondary antibody for 2 hours. The membranes were again washed for 30 minutes in TBS/Tween/Triton and anti-peptide reactivity was visualized using ECL. Specific epitope binding specificity for each of the O772P-polyclonal antibodies is described in 20 Table 5.

Table 5

SEQ ID NO:	Peptide #	Anti-O772P1	Anti-O772P2	Peptide Sequence
490	2	***	-	TCGMRRTCSTLAPGS
491	6	*	*/-	CRLTLLRPEKDGTAT
492	7	*	-	DGTATGVDAJCTHHP
493	8			CTHIPPDPKSPRLDRE
494	9	***	***	RLDREQLYWELSQLT
495	111	*/-	-	LGPYALDNDSLFVNG
496	13	****	-	SVSTTSTPGTPTYVL
497	22	-	-	LRPEKDGEATGVDAI
498	24	**	*/-	DPTGPGLDREQLYLE
499	27	*/-	-	LDRDSLYVNGFTHRS
500	40	+/-	-	GPYSLDKDSLYLNGY
501	41	-	-	YLNGYNEPGPDEPPT
502	47	***	***	ATFNSTEGVLQHLLR

10



50	T -	***	QLISLRPEKDGAATG
	-	**	GAATGVDTTCTYHPD
	-	*/-	TYHPDPVGPGLDIQQ
	-	*	LDIQQLYWELSQLTH
	-	*	HIVNWNLSNPDPTSS
59	•	*	DPTSSEYITLLRDIQ
60	-	*	LRDIQDKVTTLYKGS
61	-	***	LYKGSQLHDTFRFCL
71	-	**	DKAQPGTTNYQRNKR
	60	51 - 52 - 53 - 58 - 59 - 60 - 61 -	50 -

^{*=} relative reactive level, -; no binding, ****; maximal binding

EXAMPLE 16

IDENTIFICATION OF A NOVEL N-TERMINAL REPEAT STRUCTURE ASSOCIATED WITH O772P

Various O772P cDNA and protein forms have been identified and characterized as detailed above (e.g., Examples 1, 2, 9, and 14). Importantly, O772P RNA and protein have been demonstrated to be over-expressed in ovarian cancer tissue relative to normal tissues and thus represents an attractive target for ovarian cancer diagnostic and therapeutic applications.

Using bioinformatic analysis of open reading frames (ORFs) from genomic nucleotide sequence identified previously as having homology with O772P, multiple nucleotide repeat sequences were identified in the 5' region of the gene encoding the O772P protein. A number of these repeat sequences were confirmed by RT-PCR using primers specific for the individual repeats. Fragments which contained multiple repeats were amplified from cDNA, thus confirming the presence of specific repeats and allowing an order of these repeats to be established.

Unexpectedly, when various sets of O772P sequences derived from different database and laboratory sources were analyzed, at least 20 different repeat structures, each having substantial levels of identity with each other (see Table 6), were identified in the 5' region of the O772P gene and the corresponding N-terminal region of the O772P protein. Each repeat comprises a contiguous open reading frame encoding a polypeptide unit that is capable of being spliced to one or more other repeats such that concatomers of the repeats are formed in differing numbers and orders. Interestingly, other molecules have been described in the scientific literature that have repeating structural domains analogous to those described herein for O772P. For example, the

20

25

mucin family of proteins, which are the major glycoprotein component of the mucous which coats the surfaces of cells lining the respiratory, digestive and urogenital tracts, have been shown to be composed of tandemly repeated sequences that vary in number, length and amino acid sequence from one mucin to another (Perez-Vilar and Hill, *J. Biol. Chem. 274(45)*:31751-31754, 1999).

The various identified repeat structures set forth herein are expected to give rise to multiple forms of O772P, most likely by alternative splicing. The cDNA sequences of the identified repeats are set forth in SEQ ID NOs:513-540, 542-546, and 548-567. The encoded amino acid sequences of the repeats are set forth in SEQ ID NOs:574-593. In many instances these amino acid sequences represent consensus sequences that were derived from the alignment of more than one experimentally derived sequence.

Each of these splice forms is capable of encoding a unique O772P protein with multiple repeat domains attached to a constant carboxy terminal protein portion of O772P that contains a trans membrane region. The cDNA sequence of the O772P constant region is set forth in SEQ ID NO:568 and the encoded amino acid sequence is set forth in SEQ ID NO:594.

All of the available O772P sequences that were obtained were broken down into their identifiable repeats and these sequences were compared using the Clustal method with weighted residue weight table (MegAlign software within DNASTAR sequence analysis package) to identify the relationship between the repeat sequences. Using this information, the ordering data provided by the RT-PCR, and sequence alignments (automatic and manual) using SeqMan (DNASTAR), one illustrative consensus full length O772P contig was identified comprising 20 distinct repeat units. The cDNA for this O772P cDNA contig is set forth in SEQ ID NO:569 and the encoded amino acid sequence is set forth in SEQ ID NO:595. This form of the O772P protein includes the following consensus repeat structures in the following order:

SEQ ID NO:572- SEQ ID NO:574- SEQ ID NO:575-SEQ ID NO:576-30 SEQ ID NO:577- SEQ ID NO:578- SEQ ID NO:579- SEQ ID NO:580- SEQ ID NO:581- SEQ ID NO:582- SEQ ID NO:583- SEQ ID NO:584- SEQ ID NO:585- SEQ



ID NO:586- SEQ ID NO:587- SEQ ID NO:588- SEQ ID NO:589- SEQ ID NO:590- SEQ ID NO:591- SEQ ID NO:592- SEQ ID NO:593.

SEQ ID NO:595, therefore, represents one illustrative full-length consensus sequence for the O772P protein. As discussed above, however, based on current knowledge of this protein and based upon scientific literature describing proteins containing analogous repeating structures, many other forms of O772P are expected to exist with either more or less repeats. In addition, many forms of O772P are expected to have differing arrangements, e.g., different orders, of these N-terminal repeat structures. The existence of multiple forms of O772P having differing numbers of repeats is supported by Northern analysis of O772P. In this study, Northern hybridization of a O772P-specific probe resulted in a smear of multiple O772P-hybridizing transcripts, some in excess 10kb.

Thus, the variable repeat region of the O772 protein can be illustratively represented by the structure Xn - Y, wherein X comprises a repeat structure having at least 50% identity with the consensus repeat sequence set forth in SEQ ID NO:596; n is the number of repeats present in the protein and is expected to typically be a integer from 1 to about 35; Y comprise the O772P constant region sequence set forth in SEQ ID NO:594 or sequences having at least 80% identity with SEQ ID NO:594. Each X present in the Xn repeat region of the O772 molecule is different.

To determine the consensus sequences of each of the 20 repeat regions, sequences that were experimentally determined for a discrete repeat region were aligned and a consensus sequence determined. In addition to determining the consensus sequences for individual repeat regions, a consensus repeat sequence was also determined. This sequence was obtained by aligning the 20 individual consensus sequences. Variability of the repeats was determined by aligning the consensus amino acid sequences from each of the individual repeat regions with the over all repeat consensus sequence. Identity data is presented in Table 6.

<u>Table 6</u>

<u>Percent identities of Repeat Sequences with Reference to the Consensus Repeat Sequence</u>

Repeat Number	SEQ ID NO:	Percent Identity to
(amino acid)		Consensus Repeat
		Sequence
2	574	88
3	575	84
4	576	88
5	577	89
6	578	93
7	579	90
8	580	91
9	581	88
10	582	85
11	583	86
12	. 584	87
13	585	87
14	586	89
15	587	89
16	588	89
17	589	83
18	590	84
19	591	83
20	592	57
21	593	68

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration,

various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is Claimed:

1. An O772P polypeptide having the structure:

 $X_{n}-Y$

wherein X comprises a sequence having at least 50% identity with the consensus O772P repeat sequence set forth in SEQ ID NO: 596;

Y comprises a sequence having at least 80% identity with the O772P constant region sequence set forth in SEQ ID NO: 594;

n is an integer from 1 to 35;

wherein each X present in said polypeptide is different.

- 2. The polypeptide of claim 1, wherein X comprises a sequence selected from the group consisting of any one of SEQ ID NOs: 574-593.
- 3. The polypeptide of claim 1, wherein Y comprises the sequence set forth in SEQ ID NO: 594.
 - 4. The polypeptide of claim 1, wherein n is an integer from 15 to 25.
 - 5. The polypeptide of claim 1, wherein n is 20.
- 6. The polypeptide of claim 1, wherein said polypeptide comprises SEQ ID NO: 595.
- 7. The polypeptide of claim 1, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.
 - 8. An O772P polypeptide having the structure:

 X_n-Y



wherein X comprises an O772P repeat sequence selected from the group consisting of any one of SEQ ID NOs: 574-593;

Y comprises a sequence having at least 90% identity with the O772P constant region sequence set forth in SEQ ID NO: 594;

n is an integer from 15 to 25; wherein each X present in said polypeptide is different.

- 9. The polypeptide of claim 8, wherein n is 20.
- 10. The polypeptide of claim 8, wherein said polypeptide comprises SEQ ID NO: 595.
- 11. The polypeptide of claim 8, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.
 - 12. An O772P polypeptide having the structure:

 X_n-Y

wherein n is 20 and X comprises the following O772P repeat sequences:

SEQ ID NO: 574 - SEQ ID NO: 575 - SEQ ID NO: 576 - SEQ ID NO:

577 - SEQ ID NO: 578 - SEQ ID NO: 579 - SEQ ID NO: 580 - SEQ ID NO: 581 - SEQ

ID NO: 582 - SEQ ID NO: 583 - SEQ ID NO: 584 - SEQ ID NO: 585 - SEQ ID NO:

586 - SEQ ID NO: 587 - SEQ ID NO: 588 - SEQ ID NO: 589 - SEQ ID NO: 590 - SEQ

ID NO: 591 - SEQ ID NO: 592 - SEQ ID NO: 593; and

Y comprises the sequence set forth in SEQ ID NO: 594.

- 13. The polypeptide of claim 12, wherein said polypeptide comprises SEQ ID NO: 595.
- 14. The polypeptide of claim 12, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.



15. An O772P polynucleotide having the structure:

 X_n-Y

wherein X comprises an O772P repeat sequence selected from the group consisting of any one of SEQ ID NOs: 512-540, 542-546 and 548-567;

Y comprises a sequence having at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 568;

n is an integer from 1 to 35;

wherein each X present in said polypeptide is different.

- 16. The polynucleotide of claim 15, wherein said polynucleotide comprises SEQ ID NO: 569.
 - 17. The polynucleotide of claim 15, wherein n is from 15 to 25.
 - 18. The polynucleotide of claim 15, wherein n is 20.
- 19. The polynucleotide of claim 15, wherein said polynucleotide is overexpressed in ovarian cancer cells compared with normal tissues.
- 20. An isolated polynucleotide comprising a sequence selected from the group consisting of:
 - (a) sequences provided in SEQ ID NOs: 464-477 and 512-569;
- (b) complements of the sequences provided in SEQ ID NOs: 464-477 and 512-569;
- (c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NOs: 464-477 and 512-569;
- (d) sequences that hybridize to a sequence provided in SEQ ID NOs: 464-477 and 512-569, under highly stringent conditions;
- (e) sequences having at least 75% identity to a sequence of SEQ ID NOs: 464-477 and 512-569;



- (f) sequences having at least 90% identity to a sequence of SEQ ID NOs: 464-477 and 512-569; and
- (g) degenerate variants of a sequence provided in SEQ ID NOs: 464-477 and 512-569.
- 21. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:
 - (a) sequences encoded by a polynucleotide of claim 20; and
- (b) sequences having at least 80% identity to a sequence encoded by a polynucleotide of claim 20; and
- (c) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 20.
- 22. An expression vector comprising a polynucleotide of claim 20 operably linked to an expression control sequence.
- 23. A host cell transformed or transfected with an expression vector according to claim 22.
- 24. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 21.
- 25. A method for detecting the presence of a cancer in a patient, comprising the steps of:
 - (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 21;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

- 26. A fusion protein comprising at least one polypeptide according to claim 21.
- 27. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:
 - (a) polypeptides according to claim 21;
 - (b) polynucleotides according to claim 20; and
- (c) antigen-presenting cells that express a polynucleotide according to claim 20,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 28. An isolated T cell population, comprising T cells prepared according to the method of claim 27.
- 29. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:
 - (a) polypeptides according to claim 21;
 - (b) polynucleotides according to claim 20;
 - (c) antibodies according to claim 24;
 - (d) fusion proteins according to claim 26;
 - (e) T cell populations according to claim 28; and
- (f) antigen presenting cells that express a polypeptide according to claim 21.
- 30. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 29.

- 31. A method for the treatment of a ovarian cancer in a patient, comprising administering to the patient a composition of claim 29.
- 32. A method for determining the presence of a cancer in a patient, comprising the steps of:
 - (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide that hybridizes to a polynucelotide sequence according to claim 21 under moderately stringent conditions;
- (c) detecting in the sample an amount of said polynucleotide that hybridizes to the oligonucleotide; and
- (d) comparing the amount of said polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.
- 33. An O772 polypeptide comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 490-511.
- 34. An O8E polypeptide comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 394-415.
- 35. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 1.



11729.1 contg

11729-45.21.21.cons1

11729-45.21.21.cons2

11731.1contig

TCTTTTCTTCGATTTCCTTCAATTTGTCACGTTTGATTTTATGAAGTTGTTCAAGGGCTAACTGCTGTGTAT
TATAGCTTTCTCTGAGTTCCTTCAGCTGATTGTTAAATGAATCCATTTCTGAGAGCCTTAGATGCAGTTTCTTTT
TCAAGAGCATCTAATTGTTCTTTAAGTCTTTTGGCATAATTCTTCCTTTTCTGATGACTTTTTATGAAGTAAACT
GATCCCTGAATCAGGTGTGTTACTGAGCTGCATGTTTTTAATTCTTTCGTTTAATAGCTGCTTCTCAGGGACCA
GATAGATAAGCTTATTTTGATATTCCTTAAGCTCTTGTTGAAGTTGTTTGATTTCCATAATTTCCAGGTCACAC
TGTTTATCCAAAACTTCTAGCTCAGTCTTTTGTGTTTGCTTTCTGATTTTGGACATCTTGTAGTCTGCCTGAGAT
CTGCTGATGXTTTCCATTCACTGCTTCCAGTTCCAGGTGGAGACTTTXCTTTCTGGAGCTCAGCCTGACAATGC
CTTCTTGXTCCCT

Fig. 1A



11731.2contig

11734.1contig

AATAGATTTAATGCAGAGTGTCAACTTCAATTGATTGATAGTGGCTGCCTAGAGTGCTGTGTTGAGTAGGTTTC
TGAGGATGCACCCTGGCTTGAAGAGAAAAGACTGGCAGGATTAACAATATCTAAAATCTCACTTGTAGGAGAAAC
CACAGGCACCAGAGCTGCCACTGGTGCTGGCACCAGCTCCACCAAGGCCAGCGAAGAGCCCAAATGTGAGAGTG
GCGGTCAGGCTGGCACCAGCACTGAAGCCACCACTGGTGCTGGCACTGGCACTGGCACTGTTATTGGTACTGGT
ACTGGCACCAGTGCTGGCACTGCCACTCTCTTGGGCTTTAGCTTCTGCTCCCGCCTGGATCCGGGCTT
TGGCCCAGGGTCCGATATCAGCTTCGTCCCAGTTGCAGGCCCGGCAGCATTCTCCGAGCCGAGCCCAATGCCC
ATTCGAGCTCTAATCTCGGCCCTAGCCTTGGCTTCAGCTGCAGCCTCAGCTTCAAATCCGCTTCCAT
CGCCTCTCGGTAC

11734.2contig

GCCAAGAAAGCCCGAAAGGTGAAGCATCTGGATGGGGAAGAGGATGGCAGCAGTGATCAGAGTCAGGCTTCTGG
AACCACAGGTGGCCGAAGGGTCTCAAAGGCCCTAATGGCCTCAATGGCCCGCAGGGCTTCAAGGGGTCCCATAG
CCTTTTGGGCCCGCAGGGCATCAAGGACTCGGTTGGCTGCTTTGGGCCCGGAGAGCCTTGCTCTCCCTGAGATCA
CCTAAAGCCCGTAGGGGCAAGGCTCGCCGTAGAGCTGCCAAGCTCCAGTCATCCCAAGAGCCTGAAGCACCACC
ACCTCGGGATGTGGCCCTTTTGCAAGGGAGGCAAATGATTTGGTGAAGTACCTTTTTGGCTAAAGACCAGACGA
AGATTCCCATCAAGCGCTCGGACATGCTGAAGGACATCATCAAAGAATACACTGATGTGTACCCCGAAATCATT
GAACGAGCAGGCTATTCCTTGGAGAAAGGTATTTGGGATTCAATTGAAGGAAAATTGATAAGAATGACCACTTGTA
CATTCTTCTCAGC

11736.1contg



3/101 11736.2contig

11739-1&2

11740.1.contig

Fig. 1C



11766.1.contig

11766.2.contig

11773.2.contig

11775-182



5/101 11777.1&2.cons

11779.2.contig

11781 & 37.cons

Fig. 1E



6/101 11781-76-87-37

11784-1 & 2

11785.2.contig



7/101 11718-1&2 cons

13690.4

CAACTTATTACTTGAAATTATAATATAGCCTGTCCGTTTGCTGTTTCCAGGCTGTGATATATTTTCCTAGTGGT TTGACTTTAAAAATAAAGGTTTAATTTTCTCCCC

13693.1

13694.1

Fig. 1G



13694.2

GACTGTCCTGAACAAGGGACCTCTGACCAGAGAGCTGCAGGAGATGCAGAGTGGTGGCAGGAGTGGAAGCCAAA
GAACACCCACCTTCCTCCCTTGAAGGAGTAGAGCAACCATCAGAAGATACTGTTTTATTGCTCTGGTCAAACAA
GTCTTCCTGAGTTGACAAAACCTCAGGCTCTGGTGACTTCTGAATCTGCAGTCCACTTTCCATAAGTTCTTGTG
CAGACAACTGTTCTTTTGCTTCCATAGCAGCAACAGATGCTTTGGGGCTAAAAGGCATGTCCTCTGACCTTGCA
GGTGGTGGATTTTGCTCTTTTACAACATGTACATCCTTACTGGGCTGTCACAGGGATGTCCTTGCTGGA
CTGTTCTGCTATGGGGATATCTTCGTTGGACTGTTCTTCATGCTTAATTGCAGTATTAGCATCCACATCAGACA
GCCTGGTATAACCAGAGTTGGTGGTTACTGATTGTAGCTGCTCTTTTGTCCACTTCATATGGCACAAGTATTTTC
CTCAACATCCTGGCTCTGGGAAG

13695.1

GAAATGTATATTTAATCATTCTCTTGAACGATCAGAACTCTRAAATCAGTTTTCTATAACARCATGTAATACAG
TCACCGTGGCTCCAAGGTCCAGGAAGGCAGTGGTTAACACACATGAAGAGTGTGGGAAGGGGGGCTGGAAACAAAGT
ATTCTTTCCTTCAAAGCTTCATTCCTCAAGGCCTCAATTCAAGCAGTCATTGTCCTTGCTTTCAAAAGTCTGT
GTGTGCTTCATGGAAGGTATATGTTTGTTGCCTTAATTTGAATTGTGGCCAGGAAGGGTCTGGAGATCTAAATT
CAGAGTAAGAAACCTGAGCTAGAACTCAGGCATTTCTCTTACAGAACTTGGCTTGCAGGGTAGAATGAANGGA
AAGAAACTTAGAAGCTCAACAAGCTGAAGATAATCCCATCAGGCATTTCCCATAGGCCTTGCAACTCTGTTCAC
TGAGAGATGTTATCCTG

13695.2

13697.1

TAGCTGTCTTCCTCACTCTTATGGCAATGACCCCATATCTTAATGGATTAAGATAATGAAAGTGTATTTCTTAC
ACTCTGTATCTATCACCAGAAGCTGAGGTGATAGCCCGCTTGTCATTGTCATCCATATTCTGGGACTCAGGCGG
GAACTTTCTGGAATATTGCCAGGGAGCATGGCAGAGGGGCACAGTGCATTCTGGGGGAATGCACATTGGCTCAG
CCTGGGTAATGAGTGATATACATTACCTCTGTTCACAACTCATTGCCCAGCACCAGATCACAAGGCCCCACCAAA
TACCAGAGCCCAAGAAATGTAGTCCTGTTGATATGGTTTTTGCTGTGTCCCAACCCAAATCTCATCTTGAATTGT
AAGCTCCCATAATTCCCATGTGTTGTGGGAGGGACCTGGTG

Fig. 1H



13697.2

13699.1&2

13703.3

13705.1

Fig. 1I



13705.2

13707.4

13708.1&2

GGCGGGTAGGCATGGAACTGAGAAGAACGAAGAAGCTTTCAGACTACGTGGGGAAGAATGAAAAAACCAAAATT ATCGCCAAGATTCAGCAAAGGGGACAGGAGCTCCAGCCCGAGAGCCTATTATTAGCAGTGAGGAGCAGAAGCA GCTGATGCTGTACTATCACAGAAGACAAGAGAGACATTATCACAGAAGACAAGAGACAAGAGAGACATTTTCATGGAAGAAAAATGATGATGATGCCTATTTAA ACTCACCATGGGCGGATAACACTGCTTTGAAAAGACATTTTCATGGAGTGAAAGACATAAAGTGGAGACCAAGA TGAAGTTCACCAGCTGATGACACTTCCAAAGAGATTAGCTCACCT

13709.1



11/101 13709.2

TATGAAGAAGGGAAAAGAAGATAATTTGTGAAAGAAATGGGTCCAGTTACTAGTCTTTGAAAAAGGGTCAGTCTG
TAGCTCTTCTTAATGAGAATAGGCAGCTTTCAGTTGCTCAGGGTCAGATTTCCTTAGTGGTGTATCTAATCACA
GGAAACATCTGTGGTTCCCTCCAGTCTCTTTCTGGGGGGACTTGGGCCCACTTCTCATTTCATTTAATTAGAGGA
AATAGAACTCAAAGTACAATTTACTGTTGTTTAACAATGCCACAAAGACATGGTTGGGAGCTATTTCTTGATTT
GTGTAAAATGCTGTTTTTTGTGTGCTCATAATGGTTCCAAAAAATTGGGTGCTGGCCAAAGAGAGATACTGTTACA
GAAGCCAGCAAGAAGACCTCTGTTCATTCACACCCCCCGGGGATATCAGGAATTGACTCCAGTGTGTGCAAATCC
AGTTTGGCCTATCTTCT

13712.1&2

13714.1&2

13716.1&2

Fig. 1K



13718.2

13722.3

CATGCGTTTCACCACTGTTGGCCAGGCTGGTCTCGAACTCCTGGCCTCAAGCAATCCACCCGCCTCAGCCTCCA
AAAGTGCTGGGATTACAGATGTGAGCCATGGCACCATGCCAAAAGGCTATATTCCTGGCTCTGTGTTTCCGAGA
CTGCTTTTAATCCCAACTTCTCTACATTTAGATTAAAAAAATATTTTTATTCATGGTCAATCTGGAACATAATTAC
TGCATCTTAAGTTTCCACTGATGTATATAGAAGGCTAAAGGCACAATTTTTATCAAATCTAGTAGAGTAACCAA
ACATAAAATCATTAATTACTTTCAACTTAATAACTAATTGACATTCCTCAAAAGAGCTGTTTTCAATCCTGATA
GGTTCTTTATTTTTTCAAAAATATATTTGCCATGGGATGCTAATTTGCAATAAGGCGCATAATGAGAATACCCCA
AACTGGA

13722.4

13724-13698-13748

Fig. 1L



13730.1

13732.1

13732.2

Fig. 1M



14/101 13735.1

13735.2

13736.1

13737.1&2

Fig. 1N



15/101 13738.1

TTTGACTTTAGTAGGGGTCTGAACTATTTATTTTACTTTGCCMGTAATATTTARACCYTATATATCTTTCATTA
TGCCATCTTATCTTCTAATGBCAAGGGAACAGWTGCTAAMCTGGCTTCTGCATTWATCACATTAAAAATGGCTT
TCTTGGAAAATCTTCTTGATATGAATAAAGGATCTTTTAVAGCCATCATTTAAAGCMGGNTTCTCCCAACACG
AGTCTGCTSASGGGGGGKGAGCTGTGAACTCTGGCTGAAGGCTTTCCCATACACACTGCAATGACMTGGTTTCT
GACCAGBGTGAGTTA

13738.2

13739.1&2

GAGACAGGGTCTCACTTTGTCACCCAGGCTGGAATGCAGTGGTGCGATCTTACGTAGCTCACTGCAGCCCTGAC
CTCCTGGACTCAAACAATTCTCCTGCCTCAGCCCTGCAAGTAGCTGGGACTGTGGGTGCATGCCACCATGCCTG
GCTAACTTTTGTAAGTTTTTGTAAAGATGGGGTTTTGCCATGTTGCACATGCTGGTCTTGAACTCCTGAGCTCAA
ACGATCTGCCCACCTCGGCCTCCCAGAATGTTGGGATTACAGGGGTAAACCACCACGCCTGGCCCCATTAGGGT
ATTCTTAGCATCCACTTGCTCACTGAGATTAATCATAAGAGATGATAAGCACTGGAAGAAAAAAATTTTTACTA
GGCTTTGGATATTTTTTTCCTTTTTCAGCTTTATACAGAGGATTGGATCTTTAGTTTTCCTTTAACTGATAATA
AAACATTGAAAGGAAATAAGTTTACCTGAGATTCACAGAGGATAACCGGCATCACTCCCTTGCTCAATTCCAGTC
TTTACCACATCAATTATTTTCAGAGGTGCAGGATAAAGGCCTTTAGTCTGCTCTTTCGCACTTTTTCTTCCACTTT
TTTGTAAACCTGTTGCCTGACAAATGGAATTGACAGCGTATGCCATGACTATTCCATTTTCTCCACTTT
TCCACCCAATCCCTTGTCTCTCTTTTGGAGAGAGTCTTCTTATCAGCTAGTCCTTTTGGCAAAAGTAATT
GCAACTTCTTCTAGGTATTCTATTGTCCGTTCCACTGGTGGAACCCCTGGGACCAGGACTAAAACCTCCAG

13741.1

Fig. 10



13742.1

14351.1

14351.2

ACCTTAAAGACATAGGAGAATTTATACTGGGAGAGAAAGCTTACAAATGTAAGGTTTCTGACAAGACTTGGGAG TGATTCACACCTGGAACAACATACTGGACTTCACACTGGABAGAAACCTTACAAGTGTAATGAGTGTGGCAAAG CCTTTGGCAAGCAGTCAACACTTATTCACCATCAGGCAATTCA

14354.2

AGTCAGGATCATGATGGCTCAGTTTCCCACAGCGATGAATGGAGGGCCAAATATGTGGGCTATTACATCTGAAG
AACGTACTAAGCATGATAAACAGTTTGATAACCTCAAACCTTCAGGAGGTTACATAACAGGTGATCAAGCCCGT
ACTTTTTTCCTACAGTCAGGTCTGCCGGCCCCGGTTTTAGCTGAAATATGGGCCTTATCAGATCTGAACAAGGA
TGGGAAGATGGACCAGCAAGAGTTCTCTATAGCTATGAAACTCATCAAGTTAAAGTTGCAGGGCCAACAGCTGC
CTGTAGTCCTCCCTCCTATCATGAAACAACCCCCTATGTTCTCTCCACTAATCTCTGCTCGTTTTTGGGATGGGA
AGCATGCCCAATCTGTCCATTCATCAGCCATTGCCTCCAGTTGCACCTATAGCAACACCCCTTGTCTTCTGCTAC
TTCAGGGACCAGTATTCCTCCCCTAATGATGCCTGCT

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GTGGAGGTGAAACGGAGGCAAGAAAGGGGGCTACCTCAGGAGCGAGGGACAAAGGGGGCGTGAGGCACCTAGGC
CGCGGCACCCCGGCGACAGGAAGCCGTCCTGAACCGGGCTACCGGGTAGGGGAAGGGCCCGCGTAGTCCTCGCA
GGGCCCCAGAGCTGGAGTCGGCTCCACAGCCCCGGGCCGTCGGCTTCTCACTTCCTGGACCTCCCCGGCGCCCG
GGCCTGAGGACTGGCTCGGCGGAGGGAGAAGAGAGAACAGACTTGAGCAGCTCCCCGTTGTCTCGCAACTCCAC
TGCCGAGGAACTCTCATTTCTTCCCTCGCTCCTTCACCCCCCCACCTCATGTAGAAAAGGTGCTGAAGCGTCCGGA
GGGAAGAAGAACCTGGGCTACCGTCCTGGCCTTCCCMCCCCCTTCCCGGGGCGCTTTGGTGGGCGTGGAGTTGG
GGTTGGGGGGTGGGTGGGGGTTCTTTTTTTGGAGTGCTGGGGAACTTTTTTTCCCTTCTTCAGGTCAGGGGAAAG
GGAATGCCCAATTCAGAGAGACATGGGGGCAAGAAGGACGGGAATGGGAGAGCTTCTGGAACTTTGCAGCCGTC
ATCGGGAGGCGGCAGCTCTAACAGCAGAGAGAGCGTCACCGCTTGGTATCGAAGCACAAGCGGCATAAGTCCAAAC
ACTCCAAAGACATGGGGTTGGTGACCCCCCGAAGCAGCATCCCTGGGCACAGTTATCAAACCTTTGGTGGAGTAT
GATGATATCAGCTCTGATTCCGACACCTTCTCCGATGACATGGCCTTCAAACTAGACCGAAGGGAGAACGACGA
ACGTCGTGGATCAGATCGGAGCGACCGCCTGCACAAACATCGTCACCACCAGCACAGGCGTTCCCGGGACTTAC
TAAAAGCTAAACAGACCG

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17184.4

CAAGCGTTCCTTTATGGATGTAAATTCAAACAGTCATGCTGAGCCATCCCGGGCTGACAGTCACGTTWAAGACA CTAGGTCGGGCGCCACAGTGCCACCCAAGGAGAAGAAGAATTTGGAATTTTTCCATGAAGATGTACGGAAATCT GATGTTGAATATGAAAATGGCCCCCAAATGGAATTCCAAAAGGTTACCACAGGGGCTGTAAGACCTAGTGACCC TCCTAAGTGGGAAAGAGGAATGGAGAATAGTATTTCTGATGCATCAAGAACATCAGAATATAAAACTGAGATCA TAATGAAGGAAAATTCCATATCCAATATGAGTTTACTCAGAGACAGTAGAAACTATTCCCAGG

17185.1

TAGGAATAACAAATGTTTATTCAGAAATGGATAAGTAATACATAATCACCCTTCATCTCTTAATGCCCCTTCCT
CTCCTTCTGCACAGGAGACACAGATGGGTAACATAGAGGCATGGGAAGTGGAGGAGGACACAGGACTAGCCCAC
CACCTTCTCTCCCGGTCTCCCAAGATGACTGCTTATAGAGTGGAGGAGGAGAAACAGGTCCCCTCAATGTACCA
GATGGTCACCTATAGCACCAGCTCCAGATGGCCACGTGGTTGCAGCTGGACTCAATGAAACTCTGTGACAACCA
GAAGATACCTGCTTTGGGATGAGAGGGAGGATAAAGCCATGCAGGAGGATATTTACCATCCCTACCCTAAGCA
CAGTGCAAGCAGTGAGCCCCCGGCTCCCAGTACCTGAAAAACCAAGGCCTACTGNCTTTTGGATGCTCTTTGG
GCCACG

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17190.1



17190.2

17191.2889.2



AGCCAGATGGCTGAGAGCTGCAAGAAGAAGTCAGGATCATGATGGCTCAGTTTCCCACAGCGATGAATGGAGGG CCAAATATGTGGGCTATTACATCTGAAGAACGTACTAAGCATGATAAACAGTTTGATAACCTCAAACCTTCAGG AGGTTACATAACAGGTGATCAAGCCCGTACTTTTTTCCTACAGTCAGGTCTGCCGGCCCCGGTTTTAGCTGAAA TATGGGCCTTATCAGATCTGAACAAGGATGGGAAGATGGACCAGCAAGAGTTCTCTATAGCTATGAAACTCATC ACTAATCTCTGCTCGTTTTGGGATGGGAAGCATGCCCAATCTGTCCATTCATCAGCCATTGCCTCCAGTTGCAC CTATAGCAACACCCTTGTCTTCTGCTACTTCAGGGACCAGTATTCCTCCCCTAATGATGCCTGCTCCCCTAGTG CCTTCTGTTAGTACATCCTCATTACCAAATGGAACTGCCAGTCTCATTCAGCCTTTATCCATTCCTTC TTCAACATTGCCTCATGCATCATCTTACAGCCTGATGATGGGAGGATTTGGTGGTGCTAGTATCCAGAAGGCCC AGTCTCTGATTGATTTAGGATCTAGTAGCTCAACTTCCTCAACTGCTTCCCTCTCAGGGAACTCACCTAAGACA GGGACCTCAGAGTGGGCAGTTCCTCAGCCTTCAAGATTAAAGTATCGGCAAAAATTTAATAGTCTAGACAAAGG CTACTATTTGGACTCTGGCTGACATCGATGGTGACGGACAGTTGAAAGCTGAAGAATTTATTCTGGCGATGCAC CTCACTGACATGGCCAAAGCTGGACAGCCACTACCACTGACGTTGCCTCCCGAGCTTGTCCCTCCATCTTTCAG AGGGGGAAAGCAAGTTGATTCTGTTAATGGAACTCTGCCTTCATATCAGAAAAACACAAGAAGAAGAAGACCCTCAGA AGAAACTGCCAGTTACTTTTGAGGACAAACGGAAAGCCAACTATGAACGAGGAAACATGGAGCTGGAGAAGCGA CATTGTCAGGCTGAGCTCCAGAAAGAAAAGTCTCCACCTGGAACTGGAAGCAGTGAAATGGAAAACATCAGCAGA TCTCAGGCAGACTACAAGATGTCCAAATCAGAAAGCAAAACACAAAAGACTGAGCTAGAAGTTTTGGATAAACAG TGTGACCTGGAAATTATGGAAATCAAACAACTTCAACAAGAGCTTAAGGAATATCAAAAATAAGCTTATCT GGTCC'CTGAGAAGCAGCTATTAAACGAAAGAATTAAAAACATGCAGCTCAGTAACACACCTGATTCAGGGATCA GTTTACTTCATAAAAAGTCATCAGAAAAGGAAGAATTATGCCAAAGACTTAAAGAACAATTAGATGCTCTTGAA AAAGAAACTGCATCTAAGCTCTCAGAAATGGATTCATTTAACAATCAGCTGAAGGAACTCAGAGAAAGCTATAA TAGAGCAAAAAAAAAAAA



ATGGCAGTGACATTCACCATCATGGGAACCACCTTCCCTTTTCTTCAGGATTCTCTGTAGTGGAAGAGAGCACC CAGTGTTGGGCTGAAAACATCTGAAAGTAGGGAGAAGAACCTAAAATAATCAGTATCTCAGAGGGCTCTAAGGT GCCAAGAAGTCTCACTGGACATTTAAGTGCCAACAAAGGCATACTTTCGGAATCGCCAAGTCAAAACTTTCTAA CTTCTGTCTCTCTCAGAGACAAGTGAGAACTCAAGAGTCTACTGCTTTAGTGGCAACTACAGAAAACTGGTGTTA CCCAGAAAAACAGGAGCAATTAGAAATGGTTCCAATATTTCAAAGCTCCGCAAACAGGATGTGCTTTCCTTTTGC CCATTTAGGGTTTCTTCTCTTTTCTCTTTTATTAACCACTA



ATATCTAGAAGTCTGGAGTGAGCAAACAAGAGCAAGAAACAAAAAGAAGCCAAAAAGCAGAAGGCTCCAATATGA ACAAGATAAATCTATCTTCAAAGACATATTAGAAGTTGGGAAAATAATTCATGTGAACTAGACAAGTGTGTTAA GGAGTGAGAGGACAGGATAGTGCATGTTCTTTGTCTCTGAATTTTTAGTTATATGTGCTGTAATGTTGCTCTGA GGAAGCCCCTGGAAAGTCTATCCCAACATATCCACATCTTATATTCCACAAATTAAGCTGTAGTATGTACCCTA AGACGCTGCTAATTGACTGCCACTTCGCAACTCAGGGGCGGCTGCATTTTAGTAATGGGTCAAATGATTCACTT TTTATGATGCTTCCAAAGGTGCCTTGGCTTCTCTCCCAACTGACAAATGCCAAAGTTGAGAAAAATGATCATA ATTITAGCATAAACAGAGCAGTCGGCGACACCGATTITATAAATAAACTGAGCACCTTCTTTTTAAACAAACAA ATGCGGGTTTATTTCTCAGATGATGTTCATCCGTGAATGGTCCAGGGAAGGACCTTTCACCTTGACTATATGGC ATTATGTCATCACAAGCTCTGAGGCTTCTCCTTTCCATCCTGCGTGGACAGCTAAGACCTCAGTTTTCAATAGC ATCTAGAGCAGTGGGACTCAGCTGGGGTGATTTCGCCCCCCATCTCCGGGGGAATGTCTGAAGACAATTTTGTT ACCTCAATGAGGGAGTGGAGGATACAGTGCTACTACCAACTAGTGGATAAAGGCCAGGGATGCTCCAAC CTCCTACCATGTACAGGACGTCTCCCCATTACAACTACCCAATCCGAAGTGTCAACTGTGTCAGGACTAAGAAA GGCAAATAAGCATTCTGTCTCTTTGGCTGCCTGCCTCAGCACAGAGAGCCAGAACTCTATCGGGCACCAGGATAA CATCTCTCAGTGAACAGAGTTGACAAGGCCTATGGGAAATGCCTGATGGGATTATCTTCAGCTTGTTGAGCTTC TAAGTTTCTTTCCCTTCATTCTACCCTGCAAGCCAAGTTCTGTAAGAGAAATGCCTGAGTTCTAGCTCAGGTTT TGAAGCACACACAGACTTTTGAAAGCAAGGACAATGACTGCTTGAATTGAGGCCTTGAGGAATGAAGCTTTGAA GGAAAAGAATACTTTGTTTCCAGCCCCCTTCCCACACTCTTCATGTGTTAACCACTGCCTTCCTGGACCTTGGA GCCACGGTGACTGTATTACATGTTGTTATAGAAAACTGATTTTAGAGTTCTGATCGTTCAAGAGAATGATTAAA **TATACATTTCCTA**

Fig. 2C



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1.1.000			(422/10625 (420)	421,00186 (C117.)	100	4.5	84 18	.861 2	21 8
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Take Cate			422X0507 (42ID	Aziodise (C11)	94.28	W.	8	(443	20 50
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T. VIBOR DVBIVT).	CT19 BrainN	42200610 (420)	स्अख्लाञ्डा (द्या:	367	32	85	1278	21 88
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GCATCCACTCCGGTGGCTTCCCCCATCTTTCTCTGGCCTGAGCAAGGTCAGCCTGCAGCCAGAGTACAGAGGGCC
AACACTGGTGTTCTTGAACAAGGGCCTTAGCAGGCCCTGAAGGRCCCTCTCTGTAGTGTTGAACTTCCTGGAGC
CAGGCCACATGTTCTCCTCATACCGCAGGYTAGYGATGGTGAAGTTGAGGGTGAAATAGTATTMANGRAGATGG
CTGGCARACCTGCCCGGGCGGCCGCTCSAAATCC





Fig. 7A

AGCGTGGTCGCGGCCGAGGTCCAGTCGCAGCATGCTCTTTCTCCTGCCCACTGGCACAGTGAGGAAGATCTCTGCTGTCAGTGAGAAGGCTGTCATCCACTGAGATGGCAGTCAAAAGTGCATTTAATACACCTAACGTATCGAACATCATAGCCTTGGCCCAGGTTATCTCATATGTGCTCAGAACACTTACAATAGCCTGCAGACCTGCCCGGGCGGCCGCTCGA

Fig. 7B



TGTGGTGTTGAACTTCCTGGAGNCAGGGTGACCCATGTCCTCCCCATACTGCAGGTTGGTGATGGTGAAGTTGA GGGTGAATGGTACCAGGAGAGGGCCAGCAGCAGCCATAATTGTSGRGCKGSMGMSSGAGGMWGGWGTYYCWGAGGTT CYRARRTCCACTGTGGAGGTCCCAGGAGTGCTGGTGGTGGGCACAGAGSTCYGATGGGTGAAACCATTGACATA GAGACTGTTCCTGTCCAGGGTGTAGGGGCCCAGCTCTTYRATGYCATTGGYCAGTTKGCTYAGCTCCCAGTACA GCCRCTCTCKGYYGMGWCCAGSGCTTTTGGGGTCAAGATGATGGATGCAGATGGCATCCACTCCAGTGGCTGCT CCATCCTTCTCGGACCCTGAGAGAGGGCCAACACTGGTGTTCTTTGAATA



TCGAGCGGCCGCCCGGGCAGGTCAGGAAGCACATTGGTCTTAGAGCCACTGCCTCCTGGATTCCACCTGTGCTG CGGACATCTCCAGGGAGTGCAGAAGGGAAGCAGGTCAAACTGCTCAGATCAGACTAGACTAGCTGTTCTCAGTTC TCACCTGAGCAAGGTCAGTCTGCAGCCAGAGTACAGAGGGCCAACACTGGTGTTCTTGAACAAGGGCTTGAGCA GACCCTGCAGAACCCTCTTCCGTGGTGTTGAACTTCCTGGAAACCAGGGTGTTGCATGTTTTTCCTCATAATGC AAGGTTGGTGATGG



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11721-1

11721-2

AAGGCTGGTGGGTTTTTGATCCTGCTGAGAAACCTCCGCTTTCATGTGGAGGAAGAAGGGAAAGATGC
TTCTGGGAACAAGGTTAAAGCCGAGCCAGCCAAAATAGAAGCTTTCCGAGCTTCACTTTCCAAGCTAGGGGATG
TCTATGTCAATGATGCTTTTTGGCACTGCTCACAGAGCCCACAGCTCCATGGTAGGAGTCAATCTGCCACAGAAG
GCTGGTGGGTTTTTGATGAAGAAGGAGCTGAACTACTTTGCAAAGGCCTTGGAGAGCCCAGAGCGACCCTTCCT
GGCCATCCTGGGCGGAGCTAAAGTTGCAGACAAGATCCAGCTCATCAATAATATGCTGGACAAAGTCAATGAGA
TGATTATTGGTGGTGGAATGGCTTTTACCTTCCTTAAGGTGCTCAACAACATGGAGATTGGCACTTCTCTGTTT
GATGAAGAGGGGAGCCAAGATTGTCAAAGACCTAATGTCCAAAGCTGAGAAGAATGGTGTGAAGATTACCTTGCC
TGTTGACTTTGTCACTGCTGACAAGTTTGATGA

11724-1

11724-2

Fig. 15A



36/101 11725-32-1.2

11726-1&2

11727-182

Fig. 15B

SUBSTITUTE SHEET (RULE 26)



37/101 11728.1.40.19.19

11728.2.40.19.19

CCCGTGGGTGCCATCCACGGAGTTGTTACCTGATCTTTGGAAGCAGGATCGCCCGTCTGCACTGCAGTGGAAGC
CCCGTGGGCAGCAGTGATGGCCATCCCCGCATGCCACGGCCTCTGGGAAGGGGCAGCAACTGGAAGTCCCTGAG
ACGGTAAAGATGCAGGAGTGGCCGGCAGAGCAGTGGGCATCAACCTGGCAGGGGCCACCCAGATGCCTGCTCAG
TGTTGTGGGCCATTTGTCCAGAAGGGGACGGCAGCAGCTGTAGCTGGCTCCTCCGGGGTCCAGGCAGCAGCCA
CAGGGCAGAACTGACCATCTGGGCACCGCGTTCCAGCCACCAGCCCTGCTGTTAAGGCCACCCAGCTCACCAGG
GTCCACATGGTCTGCCTGCGTCCGACTCCGCGGTCCTTGGGCCCTGATGGTTCTACCTGCTGTGAGCTGCCCAAGACACT
GGGAAGTATGGCTGCTGCCAATGCCCAACGCCACCTGCTGCTCCGATCACCTGCACTGCCCCAAGACACT
GTGTGTGACCTGATCCAGAGTAAGTGCCTCTCCCAAGGAGAACG

11730-1

11730-2

Fig. 15C

SUBSTITUTE SHEET (RULE 26)



38/101 11732.1contig

11732.2contig

11735-1-2

11740.2.contig

Fig. 15D



39/101 11765.2&64.2.contig

CGCCTCCACCATGTCCATCAGGGTGACCCAGAAGTCCTACAAGGTGTCCACCTCTGGCCCCCGGGCCTTCAGCA
GCCGCTCCTACACGAGTGGGCCCGGTTCCCGCATCAGCTCCTCGAGCTTCTCCCGAGTGGGCAGCAGCAACTTT
CGCGGTGGCCTGGGCGGCGCGCTATGGTGGGGCCAGCGGCATCGGGAGCATCACCGCAGTTACGGTCAACCAGAG
CCTGCTGAGCCCCCTTGTCCTGGAGGTGGACCCCAACATCCAGGCCGTGCGCACCCAGGAGAAGAAGGAGCAGATCA
AGACCCTCAACAACAAGTTTGCCTCCTTCATAGACAAGGTACGGTTCCTGGAGCAGCAGCAGAACAAGATGCTGGAG
ACCAAGTGGAGCCTCCTGCAGCAGCAGAAGACGGCTCGAAGCAACATGGACCAACATGTTCGAGAGCTACATCAA
CARCCTTAGGCCGCAGCTGGAGACTCTGGGCCAGGAGAAGACTGAAGCTGAAGCTGAAGCTGAAGCTTTCGAGAACATGTACAA
CARCCTTAGGCCGGCAGCTGGAGACTCTGGGCCAGGAGAACAAGATTTGTC
CTCATCAAGAAGGATGTGGATGAAGCTTACATGAACAAGGTAGAGCTGAAGCTTCCGCCTGGAAGGCTGACCGA
CGAGATCAACTTCCTCAGGCAGCTGTATGAAGAGGAGATCCGGGAGCTTGCAGTCCCAGATCTCGGACACATCTG
TGGTGCTGTCCATGGACAACAGCCGCTCCCTGGACATGAGCATCATTGCTGAGGTCAAGGCACAGTACGAG
GATATTGCCAACCGCAGCCGGGCTGAGGCTGAGGCACAATGTACCAGG
GATATTGCCAACCGCAGCCGGGCTGAGGCTGAGACCATCATTACCAGGTCAAGTAAGAGCACAGTACAGC
TGGGAAGCACCGGGGATGACCTGCGGCCCACAAAGACTGAGATCTCTGAGATGAACCCCGGAACATCAGCCCGGCT
CCAGGCTGAGATTACAGGCCCAGAAGACTGAGATCTCTGAGATGAACCCCGGAACATCAGCCCGGCT
CCAGGCTGAGATTGAGGGCCTCAAAGGCCAGAAGACTGAGATCTCTGAGATGAACCCCGGAACATCAGCCCGGCT
CCAGGCTGAGATTTACAAGGCCCAGAAGACTTCACCAGGTCCAAGTTACCAGCCCCGCCT
CCAGGCTGAGATTACAAGGCCCAGAAGACTTCACCAGGTCAAGATCACCCCGGAACATCAGCCCCGGCT
CCAGGCTGAGATTACAAGGCCCAGAAGACTTCACCAGGTCAAGATCACCCCGGAACATCAGCCCCGGCT
CCAGGCTGAGATTACCAGGCCTCAAAGACTTCACCAGGTCAAGACCCCGGAACATCAGCCCCGGCT
CCAGGCTGAGAGCCTTCACAGGCCCACAAAGACTTCACCCGGAACCATCACCCCGCCCAT

11767.2.contig

CCCGGAGCCAGCCAACGAGCGAAAATGGCAGACAATTTTTTCGCTCCATGATGCGTTATCTGGGTCTGGAAACC
CAAACCCTCAAGGATGGCCTGGCGCATGGGGGAACCAGCCTGCTGGGGCAGGGGGCTACCCAGGGGCTTCCTAT
CCTGGGGCCTACCCCGGGCAGCACCCCCAGGGGCTTATCCTGGACAGGCACCTCCAGGCGCCTACCCTGGAGC
ACCTGGAGCTTATCCCGGAGCACCTGCACCTGGAGTCTACCCAGGGCCACCCAGCGGCCCTGGGGCCTACCCAT
CTTCTGGACAGCCAAGTGCCACCGGAGCCTACCCTGCCACTGGCCCCTATGGCGCCCCTGCTGGGCCACTGATT
GTGCCTTATAACCTGCCTTTGCCTGGGGGAGTGGTGCCTCCCATGCTGATAACAATTCTGGGCACGGTGAAGCC
CAATGCAAACAGAATTGCTTTAGATTTCCAAAGAGGGAATGATGTTGCCTTCCACTTTAACCCCACGCTTCAATG
AGAACAACAGGAGAGTCATTGGTTGCAATACAAAGCTGGATAA

11768-1&2

Fig. 15E



40/101 11768-1&2-11735-1&2

11769.1.contig

11769.2.contig

AGCGCGGTCTTCCGGCGCGAGAAAGCTGAAGGTGATGTGGCCGCCCTCAACCGACGCATCCAGCTCGTTGAGGA
GGAGTTGGACAGGGCTCAGGAACGACTGGCCACGGCCCTGCAGAAGCTGGAGGAGGCAGAAAAAAGCTGCAGATG
AGAGTGAGAGAGGAATGAAGGTGATAGAAAAACCGGGCCATGAAGGATGAGGAGAAGATGGAGATTCAGGAGATG
CAGCTCAAAGAGGCCAAGCACATTGCGGAAGAGGCTGACCGCAAATACGAGGAGGTAGCTCGTAAGCTGGTCAT
CCTGGAGGGTGAGCTGGAGAGGGCAGAGGAGCGTGCGGAGGTGTCTGAACTAAAATGTGGTGACCTGGAAGAAG
AACTCAAGAATGTTACTAACAATCTGAAATCTCTGGAGGCTGCATCTGAAAAGTATTCTGAAAAGGAGGACAAA
TATGAAGAAGAAATTAAACTTCTGTCTGACAAACTGAAAAGGAGGCTGAGACCCGTGCTGAATTTGCAGAGAGAAAC
GGTTGCAAAACTGGAAAAGAAATTGATGACCTGGAAGAGAAACTTGCCCAGC

11770.1.contig

Fig. 15F

SUBSTITUTE SHEET (RULE 26)



41/101 11770.2.contig

11773.1.contig

11778.1.contig

11778-2830-2

Fig. 15G



11782.1.contig

ATCTACGTCATCAATCAGGCTGGAGACACCATGTTCAATCGAGCTAAGCTGCTCAATATTGGCTTTCAAGAGGC
CTTGAAGGACTATGATTACAACTGCTTTGTGTTCAGTGATGTGGACCTCATTCCGATGGACGACCGTAATGCCT
ACAGGTGTTTTTCGCAGCCACGGCACATTTCTGTTGCAATGGACAAGTTCGGGTTTAGCCTGCCATATGTTCAG
TATTTTGGAGGTGTCTCTGCTCTCAGTAAACAACAGTTTCTTGCCATCAATGGATTCCCTAATAATTATTGGGG
TTGGGGAGGAGAAGATGACGACATTTTTAACAGATTAGTTCATAAAGGCATGTCTATATCACGTCCAAATGCTG
TAGTAGGGAGGTGTCGAATGATCCGGCATTCAAGAGACAAGAAAAATGAGCCCAATCCTCAGAGGTTTGACCGG
ATCGCACATACAAAGGAAACGATGCGCTTCGATGGTTTGAACTCACTTACCTACAAGGTGTTGGATGTCAGAGA
TACCCGTTATATACCCCAAATCAC

11782.2. contig

11783-1 & 2

11786.1.contig

GCTCTTCACACTTTTATTGTTAATTCTCTTCACATGGCAGATACAGAGCTGTCGTCTTGAAGACCACCACTGAC
CAGGAAATGCCACTŢTTACAAAATCATCCCCCCTTTTCATGATTGGAACAGTTTTCCTGACCGTCTGGGAGCGT
TGAAGGGTGACCAGCACATTTGCACATGCAAAAAAGGAGTGACCCCAAGGCCTCAACCACACCTTCCCAGAGCTC
ACCATGGGCTGCAGGTGACTTGCCAGGTTTGGGGTTCGTGAGCTTTCCTTGCTGCTGCGGTGGGGAGGCCCTCA
AGAACTGAGAGGCCGGGGTATGCTTCATGAGTGTTAACATTTACGGGACAAAAGCGCATCATTAGGATAAGGAA
CAGCCACAGCACTTCATGCTTGTGAGGGTTAGCTGTAGGAGCCGGTGAAAGGATTCCAGTTTATGAAAATTTAA
AGCAAACAACGGTTTTTTAGCTGGGTGGGAAAACAGGAAAACTGTGATGTCGGCCAATGACCACCATTTTTCTGCC
CATGTGAAGGTCCCCATGAAACC

Fig. 15H



11786.2.contig

CAAGCGCTTGGCGTTTGGACCCAGTTCAGTGAGGTTCTTGGGTTTTTGTGCCTTTGGGGATTTTGGTTTGACCCA
GGGGTCAGCCTTAGGAAGGTCTTCAGGAGGAGGCCGAGTTCCCCTTCAGTACCACCCCTCTCCCCACTTTCC
CTCTCCCGGCAACATCTCTGGGAATCAACAGCATATTGACACGTTGGAGCCGAGCCTGAACATGCCCCTCGGCC
CCAGCACATGGAAAACCCCCTTCCTTGCCTAAGGTGTCTGAGTTTCTGGCTCTTGAGGCATTTCCAGACTTGAA
ATTCTCATCAGTCCATTGCTCTTGAGTCTTTGCAGAGAACCTCAGATCAGGTGCACCTGGGAGAAAGACTTTGT
CCCCACTTACAGATCTATCTCCTCCCTTGGGAAGGGCAGGGAATGGGGACGGTGTATGGAGGGGAAGGGATCTC
CTGCGCCCTTCATTGCCACACTTGGTGGGACCATGAACATCTTTAGTGTCTGAGCTTCTCAAATTACTGCAATA
GGA

13691.182

13692.1&2

13693.2

Fig. 15I



44/101 13696.1-13744.1

CTTTGCAAAGCTTTTATTTCATGTCTGCGGCATGGAATCCACCTGCACATGGCATCTTAGCTGTGAAGGAGAAA GCAGTGCACGAGAAGGAATGAGTGGGCGGAACCAACGGCCTCCACAAGCTGCCTTCCAGCAGCCCCAAGGCC ATGGCAGAAGAACAAACACAAACACAAGCAAACAGAGTCTCTTCACAGCTGGAGTCTGAAAGCTCATAGTG GCATGTGTGAATCTGACAAAATTAAAAGTGTGCATAGTCCATTACATGCATAAAACACTAATAATAATCCTGTT TACACGTGACTGCAGCAGGCAGGTCCAGCTCCACCACTGCCCTCCTGCCACATCACATCAAGTGCCATGGTTTA GAGGGTTTTTCATATGTAATTCTTTTATTCTGTAAAAGGTAACAAAATATACAGAACAAAACTTTCCCTTTTTA AAACTAATGTTACAAATCTGTATTATCACTTGGATATAAATAGTATAAGCTGATC

13700.1

CAAGGGATATATGTTGAGGGTACRGRGTGACACTGAACAGATCACAAAGCACGAGAAACATTAGTTCTCTCCCT
CCCCAGCGTCTCCTTCGTCTCCCTGGTTTTCCGATGTCCACAGAGTGAGATTGTCCCTAAGTAACTGCATGATC
AGAGTGCTGKCTTTATAAGACTCTTCATTCAGCGTATCCAATTCAGCAATTGCTTCATCAAATGCCGTTTTTGC
CAGGCTACAGGCCTTTTCAGGAGAGTTTAGAATCTCATAGTAAAAGACTGAGAAAATTTAGTGCCAGACCAAGAC
GAATTGGGTGTGTAGGCTGCATTNCTTTCTTACTAATTTCAAATGCTTCCTGGTAAGCCTGCTGGGAGTTCGAC
ACAAGTGGTTTGTTTGTTTGTTCCAGATGCCACTTCAGAAAGATACCTAAAATAATCTCCTTTCATTTTCAAAGT
AGAACAC

13700.2

13701.1



13701.2

13702.2

AGCTGGCGCTAGGGCTCGGTTGTGAAATACAGCGTRGTCAGCCCTTGCGCTCAGTGTAGAAACCCACGCCTGTAAAGGCTCGGTCTTCGTCCATCTGCTTTTTTCTGAAATACACTAAGAGCAGCCACAAAACTGTAACCTCAAGGAAACCCACAAAACCTGGAGTGCCTTAATTTTTAACCAGTTTCCAATAAAACGGTTTACTACCT

13704.2-13740.2

GGAGATGAAGATGAGGAAGCTGAGTCAGCTACGGGCARGCGGGCAGCTGAAGATGATGAGGATGACGATGTCGA TACCAAGAAGCAGAAGACCGACGAGGATGACTAGACAGCAAAAAAGGAAAAGTTAAA

13706.1

GATGAAAATTAAATACTTAAATTAATCAAAAGGCACTACGATACCACCTAAAACCTACTGCCTCAGTGGCAGTA
KGCTAAKGAAGATCAAGCTACAGSACATYATCTAATATGAATGTTAGCAATTACATAKCARGAAGCATGTTTGC
TTTCCAGAAGACTATGGNACAATGGTCATTWGGGCCCAAGAGGATATTTGGCCNGGAAAGGATCAAGATAGATN
AANGTAAAG

13706.2

Fig. 15K



13707.3

13710.2

13710-1

13711.1



13711.2

TGAGACGACCACTGGCCTGGTCCCCCCTCATKTGCTGTCGTAGGACCTGACATGAAACGCAGATCTAGTGGCA
GAGAGGAAGATGATGAGGAACTTCTGAGACGTCGGCAGCTTCAAGAAGAGCAATTAATGAAGCTTAACTCAGGC
CTGGGACAGTTGATCTTGAAAGAAGAAGAGATGGAGAAAGAGAGCCGGGAAAGGTCATCTCTCTGTTAGCCAGTCGCTA
CGATTCTCCCATCAACTCAGCTTCACATATTCCATCATCTAAAACTGCATCTCTCCCTGGCTATGGAAGAAATG
GGCTTCACCGGCCTGTTTCTACCGACTTCGCTCAGTATAACAGCTATGGGGATGTCAGCGGGGGAGTGCGAGAT
TACCAGACACTTCCAGATGGCCACATGCCTGCAATGAGAATGGACCGAGGAGTGTCTATGCCCAACATGTTGGA
ACCAAAGATATTTCCATATGAAATGCTCATGGTGACCAACAGAGGCCGAAACCAAATCTCAGAGAGGTGGACA
GAA

13713.1&2

TCACTTTATTTTTCTTGTATAAAAACCCTATGTTGTAGCCACAGCTGGAGCCTGAGTCCGCTGCACGGAGACTC
TGGTGTGGGTCTTGACGAGGTGGTCAGTGAACTCCTGATAGGGAGACTTGGTGAATACAGTCTCCTTCCAGAGG
TCGGGGGTCAGGTAGCTGTAGGTCTTAGAAATGGCATCAAAGGTGGCCTTGGCGAAGTTGCCCAGGGTGGCAGT
GCAGCCCCGGGCTGAGGTGTAGCAGTCATCGATACCAGCCATCATGAG

13715.4

13717.1&2

TGAATGGGGAGGAGCTGACCCAGGAAATGGAGCTTGNGGAGACCAGGCCTGCAGGGGATGGAACCTTCCAGAAG
TGGGCATCTGTGGTGGTGCCTCTTGGGAAGGAGCAGAAGTACACATGCCATGTGGAACATGAGGGGCTGCCTGA
GCCCCTCACCCTGAGATGGGGCAAGGAGGAGCCTCCTTCATCCACCAAGACTAACACAGTAATCATTGCTGTTC
CGGTTGTCCTTGGAGCTGTGGTCATCCTTGGAGCTGTGATGGCTTTTTGTGATGAAGAGGAGGAGAAACACAGGT
GGAAAAGGAGGGGACTATGCTCTGGCTCCAGGCTCCCAGAGCTCTGATATGTCTCTCCCAGATTGTAAAGTGTG
AAGACAGCTGCCTGGTGTGGACTTGGTGACAGACAATGTCTTCACACATCTCCTGTGACATCCAGAGACCTCAG
TTCTCTTTAGTCAAGTGTCTGATGTTCCCTGTGAGTCTGCGGGCTCAAAGTGAAGAACTGTGGAGCCCAGTCCA
CCCCTGCACACCAGGACCCTATCCCTGCACTGCCCTGTGTTCCCTTCCACAGCCAACCTTGCTGCTCCAGCCAA
ACATTGGTGGACATCTGCAGCCTGTCAGCTCCATGCTACCCTGACCTTCCACACTCCCACACCTGAGAAT
AATAATTTGAATGTGGGTGGCTGGAGAGAGTGGCTCAGCGCTGACTGCTTCCACAGGTCCTGAGTTCAAATCC
CAGCAACCACATGGTGGCTCACAACCATCTGTAATGGGATCTAATACCCTCTTCTGCAGTGTCTGAAGACASCT
ACAGTGTACTTACATATAATAAATAAATAAA

Fig. 15M

SUBSTITUTE SHEET (RULE 26)



48/101 13719.1&2

13721.1

13721.2

13723.1

CATGGGTTTCACCAGGTTGGCCAGGCTGCTCTTGAACTSCTGACCTCAGGTGATCCACCCGCCTCGGCCTCCCA
AAGTGCTGGGATTACAGGCGTGAGCCACCACGCCCGGCCCCCAAAGCTGTTTCTTTTTGTCTTTAGCGTAAAGCT
CTCCTGCCATGCAGTATCTACATAACTGACGTGACTGCCAGCAAGCTCAGTCACTCCGTGGTCTTTTTCTCTTT
CCAGTTCTTCTCTCTCTCTAAGTTCTGCCTCAGTGAAAGCTGCAGGTCCCCAGTTAAGTGATCAGGTGAGGG
TTCTTTGAACCTGGTTCTATCAGTCGAATTAATCCTTCATGATGG

Fig. 15N



13723.2

13725.1

13725.2

13726.1&2



13727.1

13727.2

ACCTAGACAGAAGGTGGGTGAGGAGGACTGGTAGGAGGCTGAGGCAATTCCTTGGTAGTTTGTCCTGAAACCC
TACTGGAGAAGTCAGCATGAGGCACCTACTGAGAGAAGTGCCCAGAAACTGCTGACTGCATCTGTTAAGAGTTA
ACAGTAAAGAGGTAGAAGTGTGTTTCTGAATCAGAGTGGAAGCGTCTCAAGGGTCCCACAGTGGAGGTCCCTGA
GCTACCTCCCTTCCGTGAGTGGGAAGAGTGAAGCCCATGAAGAACTGAGATGAAGCAAGGATGGGGTTCCTGGG
CTCCAGGCAAGGGCTGTGCTCTCTGCAGCAGGGAGCCCCACGAGTCAGAAAAAAGAACTAATCATTTGTTGCA
AGAAACCTTGCCCCGGATACTAGCCGGAAAACTGGAGGCGGNGGTGGGGGCACAGGAAAGTGGAAGTGATTTGATG
GAGAGCAGAGAAGCCTATGCACAGTGGCCGAGTCCACTTGTAAAGTG

13728.182

13731.1&2



13734.1&2

13736.2

13744.2-13696.2

13746.1&2-13720.1&2



14347.1

CAGATTTTTATTTGCAGTCGTCACTGGGGCCGTTTCTTGCTGCTTATTTGTCTGCTAGCCTGCTCTTCCAGCTG CATGGCCAGGCGCAAGGCCTTGATGACATCTCGCAGGGCTGAGAAATGCTTGGCTTGCTGGGCCAGAGCAGATT CCGCTTTGTTCACAAAGGTCTCCAGGTCATAGTCTGGCTGCTCGGTCATCTCAGAGAGCTCAAGCCAGTCTGGT CCTTGCTGTATGATCTCCTTGAGCTCTTCCATAGCCTTCTCCTCCAGCTCCCTGATCTGAGTCATGGCTTCGTT AAAGCTGGACATCTGGGAAGACAGTTCCTCCTCTTCCTTGGATAAATTGCCTGGAATCAGCGCCCCGTTAGAGC AGGCTTCCATCTCTTCTGTTTCCATTTGAATCAACTGCTCTCCACTGGGCCCACTGTGGGGGCTCAGCTCCTTG ACCCTGCTGCATATCTTAAGGGTGTTTAAAGGATATTCACAGGAGCTTATGCCTGGT

14347.2

14348.2&14350.1&2

14349.1&2

Fig. 15R



53/101 14352.1&2

14353.1

14353.2

17182.182



17183.2

GGTTCACAGCACTGCTGCTTGTGTTGTCCGGCCAGGAATTCCAGGCTCACAAGGCTATCTTAGCAGCTCGTTC
TCCGGTTTTTAGTGCCATGTTTGAACATGAAATGGAGGAGAGAGCAAAAAGAATCGAGTTGAAATCAATGATGTGG
AGCCTGAAGTTTTTAAGGAAATGATGTGCTTCATTTACACGGGGAAGGCTCCAAACCTCGACAAAATGGCTGAT
GATTTGCTGGCAGCTGCTGACAAGTATGCCCTGGAGCGCTTAAAGGTCATGTGTGAGGATGCCCTCTGCAGTAA
CCTGTCCGTGGAGAACGCTGCAGAAATTCTCATCCTGGCCGACCTCCACAGTGCAGATCAGTTGAAAACTCAGG
CAGTGGATTTCATCAACTATCATGCTTCGGATGTCTTGGAGACCTCTTGGG

17186.1&2

17187,182

17191.1889.1



55/101 17192.1&2

17193



56/101 16443.1.edit

16443.2.edit

16444.2.edit

AGCGTGGTTNCGGCCGAGGTCCCAACCAAGGCTGCANCCTGGATGCCATCAAAGTCTTCTGCAACATGGAGACT GGTGAGACCTGCGTGTACCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAGGA CAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGACC CTGCCGATGTGGACCTGCCCGGGCGGNCGCTCGA

16445.1.edit

AGCGTGGTCGCGGCCGAGGTCAAGAACCCCGCCCGCACCTGCCGTGACCTCAAGATGTGCCACTCTGACTGGAA GAGTGGAGAGTACTGGATTGACCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAGA CTGGTGAGACCTGCGTGTACCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAG GACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGA CCCTGCCGATGTGGACCTGCCCGGGCGGCCGCTCGA

Fig. 15V



16445.2.edit

16446.1.edit

TCGAGCGGCCGCCGGGCAGGTCCTCCTCAGAGCGGTAGCTGTTCTTATTGCCCCGGCAGCCTCCATAGATNAA GTTATTGCANGAGTTCCTCTCCACGTCAAAGTACCAGCGTGGGAAGGATGCACGGCAAGGCCCAGTGACTGCGT TGGCGGTGCAGTATTCTTCATAGTTGAACATATCGCTGGAGTGGACTTCAGAATCCTGCCTTCTGGGAGCACTT GGGACAGAGGAATCCGCTGCATTCCTGCTGGTGGACCTCGGCCGCGACCACGCT

16446.2.edit

16447.1.edit

Fig. 15W



16447.2.edit

16449.1.edit

16450.1.edit

16450.2.edit

Fig. 15X



16451.1.edit

16451.2.edit

TCGAGCGGCCGCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGNTGACAGAGTTGCCCACCGGTAACAACCTCTTCCCGAACCTTATGCC
TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGTACCTCTGGTGAGGACCTCGGCCGCACCACG
CT

16452.1.edit

16452.2.edit

Fig. 15Y



16453.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGCCGAACTGCCAGTGTACAGGGAAGATGTACATGTTATAGNTCTTCTCGAA GTCCCGGGCCAGCAGCTCCACGGGGTGGTCTCCTGCCTCCAGGCGCTTCTCATTCTCATGGATCTTCTTCACCC GCAGCTTCTGCTTCTCAGTCAGAAGGTTGTTGTCCTCATCCCTCTCATACAGGGTGACCAGGACGTTCTTGAGC CAGTCCCGCATGCGCAGGGGGAATTCGGTCAGCTCAGAGTCCAGGCAAGGGGGGATGTATTTGCAAGGCCCGAT GTAGTCCAAGTGGAGCTTGTGGCCCTTCTTGGTGCCCTCCAAAGTGCACTTTGTGGCAAAGAAGTGGCAGGAAG AGTCGAAGGTCTTGTTGTCATTGCTGCACACCTTCTCAAACTCGCCAATGGGGGCTGGGCAGACCTGCCCGGGC

16453.2.edit

16454.1.edit

AGCGTGGNTGCGGACGACGCCCACAAAGCCATTGTATGTAGTTTTANTTCAGCTGCAAANAATACCNCCAGCAT CCACCTTACTAACCAGCATATGCAGACA

16454.2.edit

TCGAGCGGTCGCCCGGGCAGGTCTGGCCGGATAGCACCGGGCATATTTTGGAATGGATGAGGTCTGGCACCCTG
AGCAGCCCAGCGAGGACTTGGTCTTAGTTGAGCAATTTGGCTAGGAGGATAGTATGCAGCACGGTTCTGAGTCT
GTGGGATAGCTGCCATGAAGNAACCTGAAGGAGGCGCTGGCTGGTANGGGTTGATTACAGGGCTGGAACAGCT
CGTACACTTGCCATTCTCTGCATATACTGGNTAGTGAGGCGAGCCTGGCGCTCTTCTTTGCGCTGAGCTAAAGC
TACATACAATGGCTTTGNGGACCTCGGCCGCCGACCACGCTT

Fig. 15Z



61/101 16455.1.edit

TCGAGCGGCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCCCAATCTTGTAGTTCACACCAT
TGTCATGACACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGC
CTCTGCTGGTCTTTCAAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCACCA
CGCT

16455.2.edit

16456.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGCTTNCTGCTCANGTGATTATCCTGAACCATCCAGGCCAAATAAGCGCCGGCTATGCCCCTGNATTGGATTGCCACACGGCTCACATTGCATGCAAGTTTGCTGAGCTGAAGGAAAAGATTGATC

16456.2.edit

Fig. 15AA



16459.1.edit

16459.2.edit

16460.1.edit

TCGAGCGGCCGCCCGGGCAGGTCCATTTTCTCCCTGACGGNCCCACTTCTCTCCAATCTTGTAGTTCACACCAT TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACCGGTAACAACCTCNTCCCCGAACCTTATGC CTCTGCTGGGCTTTCAGNGCCTCCACTATGATGNTGTAGGGGGGCACCTCTGGNGANGACCTCGGCCGCGACCA CGCT

16460.2.edit

Fig. 15BB



63/101 16461.1.edit

16461.2.edit

16463.1.edit

AGCGTGGNNGCGGCCGAGGTATAAATATCCAGNCCATATCCTCCCTCCACACGCTGANAGATGAAGCTGTNCAA AGATCTCAGGGTGGANAAAACCAT

16463.2.edit

Fig. 15CC



16464.1.edit

CGAGCGGCGACCGGGCAGGTNCAGACTCCAATCCANANAACCATCAAGCCAGATGTCAGAAGCTACACCATCA
CAGGTTTACAACCAGGCACTGACTACAAGANCTACCTGCACACCTTGAATGACAATGCTCGGAGCTCCCCTGTG
GTCATCGACGCCTCCACTGCCATTGATGCACCATCCAACCTGCGTTTCCTGGCCACCACACCCAATTCCTTGCT
GGTATCATGGCAGCCGCCCACGTGCCAGGATTACCGGTACATCATCNAGTATGANAAGCCTGGGCCTCCTCCCAG
AGAAGNGGTCCCTCGGCCCCGCCCTGNTGTCCCCANAGGNTACTATTACTGNGCCNGCAACCGGCAACCGATATC
NATTTTGNCATTGGCCTTCAACAATAATTA

16464.2.edit

AGCGTGGTTCGCGGCCGANGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTTC
TTCATCAGNGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGGCCCCATGAGATGGTTG
TCTGAGAGAGAGGCTTCTTGNCCTGTCTTTTTCCTTCCAATCAGGGGCTCGCTCTTCTGATTATTCTTCAGGGCA
ATGACATAAATTGTATATTCGGGTCCCGGNTCCAGGCCAGTAATAGTANCCTCTGTGACACCAGGGCGGNGCCG
AGGGACCACTTCTCTGGGAGGAGACCCAGGCTTCTCATACTTGATGATGAACCGGTAATCCTGGCACGTGGCG
GCTGCCATGATACCAGCAAGGAATTGGGGTGTGGTGGCCAGGAAACGCAGGTTGGATGGNGCATCAATGGCAGT
GGAGGCCGTCGATGACCACAGGGGGAGCTCCGACATTGTCATTCAAGGTG

16465.1.edit

AGCGTGGNCGCGGCCGAGGTGCAGCGGGGCTGTGCCACCTTCTGCCCCAACGATAAGGAGGGTNCCTGCCCCAGGAGAACATTAACTNTCCCCAGCTCGGCCTCTGCCGG

16465.2.edit

16466.2.edit

TCGAGCGGCCGCCCGGGCAGGTCCACCATAAGTCCTGATACAACCACGGATGAGCTGTCAGGAGCAAGGTTGAT
TTCTTTCATTGGTCCGGNCTTCTCCTTGGGGGNCACCCGCACTCGATATCCAGTGAGCTGAACATTGGGTGGCG
TCCACTGGGCGCTCAGGCT

16467.2.edit

TCGAGCGGTTCGCCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCCACGTGCCAGGA TTACCGGCTACATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGCGGTCCCTCGGCCCCGCCCTGGT GTCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGNCCTGAAGAATAA TCANNAANAGCGANCCCCTGATTGGAAGGA

Fig. 15DD



65/101 01 16469.edit

02 16469.edit

03_16470.edit

04 16470.edit

TCGAGCGGCCGCCCGGGCAGGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTT
CTTCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGGCCCATGAGATGGTT
GTCTGAGAGAGAGAGCTTCTTGTCCTACATTCGGCGGGTATGGTCTTGGCCTATGCCTTATGGGGGTGGCCGTTGT
GGGCGGTGTGGTCCGCCTAAAACCATGTTCCTCAAAGATCATTTGTTGCCCAACACTGGGTTGCTGACCAGAAG
TGCCAGGAAGCTGAATACCATTTCACCTCGGCCGCGACCACGCTA

05 16471.edit

TCGAGCGCCCCGGGCAGGTCTCCCTTCTTGCGGCCCAGGGGCAGCGCATAGTGGGACTCGTACCACTGTCG
GTACGGTGTGCTGTCGATGAGCACGATGCAATTCTTCACCAGGGTCTTGGTACGAACCAGCTCGTTATTAGATG
CATTGTAGACAACATCGATGATCCTTGTTTTACGAGTACAACACTCTGAGCCCCAGGAGAAATTCCCCACGTCC
AACCTCAGGGCACGGTATTTCTTGTTACCTCCCCGCACACGGACTGTGTGGATGCGGCGGGGGCCAAGCTGACT
CCTGAGGAAGAAGAGAGATTTTAAACAAAAAACGATCTAAAAAAATTCAGAAGAAATATGATGAAAGGAAAAAAGAA
TGCCAAAATCAGCAGTCTCCTGGAGGAGCAGTTCCAGCAGGGCAAGCTTCTTGCGTGCATCGCTTCAAGGCCGG
GACAGTGTGACCGAGCAGATGGCTATGTGCTAGAGGGCAAAGAAGTGGAGTTCTATCTTAAGAAAATCAGGGCC
CAGAATGGTGNGTCTTCAACTAATCCAAAGGGGAGTTTCAGACCAGTGCAATCAGCAAAAACATTGATACTGNT
GGCCAAATTTATTGGTGCAGGGCTTGCACANTANGANNGGCTGGGTCTTGGGGCTTGGATTGGNACAAGCTTTTG
GCAGCCTTTTTCTTTGGTTTTTGCCAAAAACCTTTTGNTGAAGANGANACCTNGGGCGGACCCCTTAACCGATTCC
ACNCCNGGNGGCGTTCTANGGNCCCNCTTG

Fig. 15EE



66/101 06 16471.edit

AGCGTGGTCGCGGCCGAGGTCTGCTGCTTCAGCGAAGGGTTTCTGGCATAACCAATGATAAGGCTGCCAAAGAC
TGTTCCAATACCAGCACCAGAACCAGCCACTCCTACTGTTGCAGCACCCTGCACCAATAAATTTGGCAGCAGTAT
CAATGTCTCTGCTGATTGCACTGGTCTGAAACTCCCTTTGGATTAGCTGAGACACCACTCTTGGGCCCTGATT
TTCCTAAGATAGAACTCCAACTCTTTGCCCTCTAGCACATAGCCATCTGCTCGGTCACACTGTCCCGGCCTTGA
AGCGATGCACGCAAGAAGCTTGCCCTGCTGGAACTGCTCCTCCAGGAGACCTGCTGATTTTTGCC
TTTCATCATATTTCTTCTGAATTTTTTTAGATCGTTTTTTGTTTAAAATCTCTTCTTCCTCAGGAGTCAGCTTG
GCCCCCGCCGCATCCACACAGTCCGTGTGCGGGGAGGTAACAAGAAATACCGTGCCCTGAGGTTGGACGTGGGG
AATTTCTCCTGGGGCTCAGAGTGCTGTACTCGTAAAACAAGGATCATCGATGGTGNCTACAATGCATCTAATAA
CGAGCTGGGTCGGACCCAAAGAACCTGGNGAANAAATGGATCGNCTCATCGACAGGACACCGTACCCGACAGGG
GNACGANTCCCACTATGCGCTTGCCCCTGGGCCGCAANAAAGGAAAACTGCCCGGGCGCCCNTCGAAAGCCCAA
TTNTGGAAAAAAATCCATCACACTGGGNGGCCNGTCGAGCATGCATNTANAGGGGCCCCATTCCCCCTNANN

07 16472.edit

TCGAGCGGCCGCCCGGGCAGGTCCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAGACTGGTGAGACCTGCGTGTACCCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAGAACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGACCTGCCGATGTGGACCTCGGCCGACCACGCT

08_16472.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA GCCTTGGTTGGGGACCTGCCCGGGCGGCCGCTCGA

09 16473.edit

Fig. 15FF



67/101 11 16474.edit

12 16474.edit

13 16475.edit

TCGAGCGCCGCCGGGCAGGTCTGGTCCAGGATAGCCTGCGAGTCCTCCTACTGCTACTCCAGACTTGACATC
ATATGAATCATACTGGGGAGAATAGTTCTGAGGACCAGTAGGGCATGATTCACAGATTCCAGGGGGGCCCAGGAG
AACCAGGGGACCCTGGTTGTCCTGGAATACCAGGGTCACCATTTCTCCCAGGAATACCAGGAGGCCTGGATCT
CCCTTGGGGCCTTGAGGTCCTTGACCATTAGGAGGCGAGTAGGAGCAGTTGGAGGCTGTGGGCAAACTGCACA
ACATTCTCCAAATGGAATTTCTGGGTTGGGGCAGTCTAATTCTTGATCCGTCACATATTATGTCATCGCAGAGA
ACGGATCCTGAGTCACAGACACATATTTGGCATGGTTCTGGCTTCCAGACATCTCTATCCGNCATAGGACTGAC
CAAGATGGGAACATCCTCCTTCAACAAGCTTNCTGTTGTGCCAAAAATAATAGTGGGATGAAGCAGACCGAGAA
GTANCCAGCTCCCCTTTTTGCACAAAGCNTCATCATGTCTAAATATCAGACATGAGACTTCTTTGGGCAAAAAAA
GGAGAAAAAGAAAAAGCAGTTCAAAGTANCCNCCATCAAGTTGGTTCCTTGCCCNTTCAGCACCCGGGCCCCGT
TATAAAACACCTNGGGCCGGACCCCCCTT

Fig. 15GG



68/101 14 16475.edit

15_16476.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGE
TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA
CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA
GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGTGC
GGGCGGGGTTCTTGCGGCTGCCCTCTGGGCTCCGGATGTTCTCGATCTGCTGGCTCAGGCTCTTGAGGGTGGTC
TCCACCTCGAGGTCACGGACCACACATTGGCATCATCAGCCCGGTAGTAGCGGCCACCATCGTGAGCCTT
CTCTTGANGTGGCTGGGGCAGGAACCTGAAGTCGAAACCAGCGCTGGGAGGACCAGAGGGCCCACCANAGGTCCAGC
AAGGGCCCGGGGGGGACCAACAGGACCAGCATCACCAAGTGCGACCCGCGAGAACCTGCCCGGCCGNCCGCTCC
AA

16 16476.edit

Fig. 15HH



69/101 17 16477.edit

18 16477.edit

AGCGTGGTTNGCGGCCGAGGTCTGGGCCAGGGGCACCAACACGTCCTCTCACCAGGAAGCCCACGGGCTCCT GTTTGACCTGGAGTTCCATTTTCACCAGGGGCACCAGGTTCACCCTTCACACCAGGAGCACCGGGCTGTCCCTT CAATCCATNCAGACCATTGTGNCCCCTAATGCCTTTGAAGCCAGGAAGTCCAGGAGTTCCAGGGAAACCACCGA GCACCCTGTGGTCCAACAACTCCTCTCTCACCAGGTCGTCCGGGTTTTTCCAGGGTGACCATCTTCACCAGCCTT GCCAGGAGGACCAGCAGGACCAGCGTTACCAACCTGCCCGGGCCGCCCCTCGA

21 16479.edit

TCGAGCGGCCGCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACCGGTAACAACCTCTTCCCGAACCTTATGCC
TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCACCACG
CT

22 16479.edit



70/101 24 16480.edit

TCGAGCGNNCGCCCGGGCAGGTCCAGTAGTGCCTTCGGGACTGGGTTCACCCCCAGGTCTGCGGCAGTTGTCAC
AGCGCCAGCCCCGCTGGCCTCCAAAGCATGTGCAGGAGCAAATGGCACCGAGATATTCCTTCTGCCACTGTTCT
CCTACGTGGTATGTCTTCCCATCATCGTAACACGTTGCCTCATGAGGGTCACACTTGAATTCTCCTTTTCCGTT
CCCAAGACATGTGCAGCTCATTTGGCTGGCTCTATAGTTTGGGGAAAGTTTGTTGAAACTGTGCCACTGACCTT
TACTTCCTCCTTCTCTACTGGAGCTTTCGTACCTTCCACTTCTGCTGTTGGTAAAATGGTGGATCTTCTATCAA
TTTCATTGACAGTACCCACTTCTCCCAAACATCCAGGGAAAATAGTGATTTCAGAGCGATTAGGAGAACCAAATT
ATGGGGCAGAAATAAGGGGCTTTTCCACAGGTTTTCCTTTGGAGGAAAGTTTCAGTGGTGACTTTAAAAGAATA
CTCAACAGTGTCTTCATCCCCATAGCAAAAGAAGAAACNGTAAATGATGGAANGCTTCTGGAGATGCCNNCATT
TAAGGGACNCCCAGAACTTCACCATCTACAGGACCTACTTCAGTTTACANNAAGNCACATANTCTGACTCANAA
AGGACCCAAGTAGCNCCATGGNCAGCACTTTNAGCCTTTCCCCTGGGGAAAANNTTACNTTCTTAAANCCTNGG
CCNNGACCCCCTTAAGNCCAAATTNTGGAAAAANTTCCNTNCNNCTGGGGGGCNGTTCNACATGCNTTTNAAGGG

25_16481.edit

26 16481.edit

27_16482.edit

TCGAGCGCCCCGGGCAGGTTGAATGGCTCCTCGCTGACCACCCCGGTGCTGGTGGTGGGTACAGAGCTCCG ATGGGTGAAACCATTGACATAGAGACTGTCCCTGTCCAGGGTGTAGGGGCCCAGCTCAGTGATGCCGTGGGTCA GCTGGCTCAGCTTCCAGTACAGCCGCTCTCTGTCCAGTCCAGGGCTTTTGGGGTCAGGACGATGGGTGCAGACA GCATCCACTCTGGTGGCTGCCCCATCCTTCTCAGGCCTGAGCAAGGTCAGTCTGCAACCAGAGTACAGAGAGCC GACACTGGTGTTCTTGAACAAGGGCATAAGCAGACCCTGAAGGACACCTCGGCCGCGACCACGCT

Fig. 15JJ



28 16482.edit

29_16483.edit

31_16484.edit

37 16487.edit

AGCGTGGTCGCGGCCGAGGTCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCT CCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGAGA GTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTC AGTCTTCCTCTTCCCCCGCATCCCCCTTCCAAACCTGCCCGGGCGGCCGCTCG

Fig. 15KK



72/101 38 16487.edit

CGAGCGGCCGGCCGGGCAGGTTTGGAAGGGGGATGCGGGGGAAGAGAGAAGACTGACGGTCCCCCAGGAGTTCA GGTGCTGGGCACGGTGGGCATGTGTGAGGTTTTGTCACAAGATTTGGGCTCAACTCTCTTGTCCACCTTGGTGTT GCTGGGCTTGTGATCTACGTTGCAGGTGTAGGTCTGGGTGCCGAAGTTGCTGGAGGGCACGGTCACCACGCTGC TGAGGGAGTAGAGTCCTGAGGACTGTAGGACAGACCTCGGCCGCCGACCACGCT

39_16488.edit

NGGNNGGTCCGGNCNGNCAGGACCACTCNTCTTCGAAATA

41 16489.edit

AGCGTGGTCGCGGCCGAGGTCCTCACTTGCCTCCTGCAAAGCACCGATAGCTGCGCTCTGGAAGCGCAGATCTG
TTTTAAAGTCCTGAGCAATTTCTCGCACCAGACGCTGGAAGGGAAGTTTGCGAATCAGAAGTTCAGTGGACTTC
TGATAACGTCTAATTTCACGGAGCGCCACAGTACCAGGACCTGCCCGGGCGGCCGCTCGA

42 16489.edit

45_16491.edit

TCGAGCGGCCGCCCGGGCAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC GGTCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCA CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG CAGCCTTGGTTGGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT GCGGGCGGGGTTCTTGACCTCGGCCGCACCACGCT

Fig. 15LL



73/101 46_16491.edit

47 16492.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAGTAACCACCACTCCCAAAAATGGACCAGGAC
CAACAAAAACTAAAACTGCAGGTCCAGATCAAACAGAAATGACTATTGAAGGCTTGCAGCCCACAGTGGAGTAT
GTGGTTAAGTGTCTATGCTCAGAATCCAAGCGGAGAGAAGTCAGCCTCTGGTTCAGACTGNAAGTAACCAACAT
TGATCGCCTAAAGGACTGGCATTCACTGATGNGGATGCCGATTCCATCAAAATTGNTTGGGAAAAACCCAACAGGG
GCAAGTTTNCANGTCNAGGNGGACCTACTCGAGCCCTGAGGATGGAATCCTTGACTNTTCCTTNNCCTGATGGG
GAAAAAAAAACCTTNAAAACTTGAAGGACCTGCCCGGGCGGCCGTNCAAAACCCAATTCCACCCCCTTTGGGGGCG
TTCTATGGGNCCCACTCGGACCAAACTTGGGGTAAN

48 16492.edit

Fig. 15MM



74/101 49_16493.edit

55_16496.edit

56_16496.edit

TCGAGCGGCCGCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCGACCACG CT

59_16498.edit

TCGAGCGGCCGCCCGGGCAGGTCCACCATAAGTCCTGATACAACCACGGATGAGCTGTCAGGAGCAAGGTTGAT
TTCTTTCATTGGTCCGGTCTTCTCCTTGGGGGTCACCCCGCACTCGATATCCAGTGAGCTGAACATTGGGTGGTG
TCCACTGGGCGCTCAGGCTTGTGGGTGTGACCTGAGTGAACTTCAGGTCAGTTGGTGCAGGAATAGTGGTTACT
GCAGTCTGAACCAGAGGCTGACTCTCTCCGCTTGGATTCTGAGCATAGACACTAACCACATACTCCACTGTGG
CTGCAAGCCTTCAATAGTCATTTCTGTTTGATCTGGACCTGCAGTTTTAGTTTTTGTTGGTCCTGGTCCATTTT
TGGGAGTGGTGACTCTCTGTAACCAGTAACAGGGGAACTTGAAGGCAGCCACTTGACACTAATGCTGTTGTCC
TGAACATCGGTCACTTGCATCTGGGATGGTTTGNCAATTTCTGTTCGGTAATTAATGGAAATTGGCTTGCTGCT
TGCGGGGCTGTCTCCACGGCCAGTGACAGCATACACAGNGATGGNATNATCAACTCCAAGTTTAAGGCCCTGAT
GGTAACTTTAAACTTGCTCCCAGCCAGNGAACTTCCGGACAGGGTATTTCTTCTGGTTTTCCGAAAGNGANCCT
GGAATNNTCTCCTTGGANCAGAAGGANCNTCCAAAACTTGGGCCGGAACCCCTT

Fig. 15NN



75/101 60 16473.edit

60 16498.edit

61 16499.edit

AGCGTGGTCGCGGCCGAGGTCNAGGA

62 16483.edit

Fig. 1500



76/101 63_16500.edit

AGCGTGGTCGCGGCCGAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCATTG
TCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTAAA
GCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGAGT
CATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCCTC
TGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTGCCCGGGCGCCCCGCT
CGA

64 16493.edit

64 16500.edit



16501.edit

16501.2.edit

GAGGACTGGCTCAGCTCCCAGTATAGCCGCTCTCTGTCCAGTCCAGGACCAGTGGGATCAAGGCGGAGGGTGCA GATGGCGTCCACTCCAGTGGCTGCCCCATGTTTCTCAAGTCTGAGCAAAGNCAGTCTGCAGCCAGAGTACAGAG GGCCAACACTGGTGCTCTTGAACAGGGACCTGAGCAGGCCCTGAAGGACCCTCTCCGTGGTGTTGAACTTCCTG GAGCCAGGGTGCTGCATGTTCTCCTCATACCGCAGGTTGTTGATGGTGAAGTTCAGTGTGAATGGCTCCTCGCT GACCACCC

16502.1.edit

16502.2.edit

Fig. 15QQ



78/101 16503.1.edit

16503.2.edit

AAGCGGCCGCCCGGGCAGGNNCAGNAGTGCCTTCGGGACTGGGNTCACCCCCAGGTCTGCGGCAGTTGTCACAG
CGCCAGCCCGCTGGCCTCCAAAGCATGTGCAGGAGCAAATGGCACCGAGATATTCCTTCTGCCACTGTTCTCC
TACGTGGTATGTCTTCCCATCATCGTAACACGTTGCCTCATGAGGGTCACACTTGAATTCTCCTTTTCCGTTCC
CAAGACATGTGCAGCTCATTTGGCTGGCTCTATAGTTTGGGGAAAGTTTGTTGAAACTGTGCCACTGACCTTTA
CTTCCTCCTTCTCTACTGGAGCTTTCCGTACCTTCCACTTCTGCTGNTGGNAAAAAGGGNGGAACNTCTTATCA
ATTTCATTGGACAGTANCCCNCTTTCTNCCCAAAACATNCAAGGGAAAATATTGATTNCNAGAGCGGATTAAGG
AACAACCCNAATTATGGGGGCCCAGAAATAAAGGGGGGCTTTTCCACAGGTNTTTTCCT

16504.1.edit

TCGAGCGGCCGCCCGGGCAGGTCTGCAGGCTATTGTAAGTGTTCTGAGCACATATGAGATAACCTGGGCCAAGC TATGATGTTCGATACGTTAGGTGTATTAAATGCACTTTTGACTGCCATCTCAGTGGATGACAGCCTTCTCACTG ACAGCAGAGATCTTCCTCACTGTGCCAGTGGGCAGGAGAAAGAGCATGCTGCGACTGGACCTCGGCCGCGACCA CGCT

16504.2.edit

AGCGTGGTCGCGGCCGAGGTCCAGTCGCAGCATGCTCTTTCTCCTGCCCACTGGCACAGTGAGGAAGATCTCTG CTGTCAGTGAGAAGGCTGTCATCCACTGAGATGGCAGTCAAAAGTGCATTTAATACACCTAACGTATCGAACAT CATAGCTTGGCCCAGGTTATCTCATATGTGCTCAGAACACTTACAATAGCCTGCAGACCTGCCCGGGCGGCCGC TCGA

Fig. 15RR



79/101 16505.1.edit

CGAGCGGCCGCCCGGGCAGGTCCAGACTCCAATCCAGAGAACCACCAAGCCAGATGTCAGAAGCTACACCATCA
CAGGTTTACAACCAGGCACTGACTACAAGATCTACCTGTACACCTTGAATGACAATGCTCGGAGCTCCCCTGTG
GTCATCGACGCCTCCACTGCCATTGATGCACCATCCAACCTGCGTTTCCTGGCCACCACACCCAATTCCTTGCT
GGTATCATGGCAGCCGCCACGTGCCAGGATTACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCA
GAGAAGTGGTCCCTCGGCCCCGCCCTGGTGNCACAGAAGCTACTATTACTGGCCTGGAACCGGGAACCGAATAT
ACAATTTATGTCATTGCCCTGAAGAATAATCANAAGAGCGAGCCCCTGATTGGAAGG

16505.2.edit

16506.1.edit

16506.2.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGTGC GGGCGGGGTTCTTGCGGCTGCCCTCTGGGCTCCGGATGTTCTCGATCTGCTGGCTCAAGCTCTTGAAGGGTGGT GTCCACCTCGAGGTCACGAAACCTGCCCGGGCGGCCGCTCGA

Fig. 15SS



16507.1.edit

AGCGTGGTCGCGGCCGAGGTCAAGAACCCCGCCCGCACCTGCCGTGACCTCAAGATGTGCCACTCTGACTGGAA
GAGTGGAGAGTACTGGATTGACCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAGA
CTGGTGAGACCTGCGTGTACCCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAG
GACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGA
CCCTGCCGATGTGGACCTGCCCGNGCCGGNCCGCTCGAAAAGCCCNAATTTCCAGNCACACTTGGCCGGCCGTT
ACTACTG

16507.2.edit

TCGAGCGGCCGCCGGGCAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCTCGGCCGCACCACGCT

16508.1.edit

16508.2.edit

Fig. 15TT



16509.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAAC AGGAGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCAGCAAGCCAATT TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAAGTAACCACCACTCCCAAAAATGGACCAGGA CCAACAAAAACTAAAACTGCAGGTCCAGATCAAACAGAAAAATGGACTATTGAAGGCTTGCAGCCCACAGTGGAA GTATGTGGNTAGGNGTCTATGCTCAGAATCCCAAGCCGGAGAAAGTCAGCCTTCTGGTTTAGACTGCAGTAACC AACATTGATCGCCCTAAAGGACTGGNCATTCACTTGGATGGTGGATGTCCAATTC

16509.2.edit

TCGAGCGGCCCCGGGCAGGTCCTTGCAGCTCTGCAGNGTCTTCTTCACCATCAGGTGCAGGGAATAGCTCAT
GGATTCCATCCTCAGGGCTCGAGTAGGTCACCCTGTACCTGGAAACTTGCCCCTGTGGGCTTTCCCAAGCAATT
TTGATGGAATCGACATCCACATCAGNGAATGCCAGTCCTTTAGGGCGATCAATGTTGGTTACTGCAGTCTGAAC
CAGAGGCTGACTCTCTCCGCTTGGATTCTGAGCATAGACACTAACCACATACTCCACTGTGGGCTGCAAGCCTT
CAATAGTCATTTCTGTTTGATCTGGACCTGCAGTTTTAAGTTTTTTGGTGGTCCTGNCCCATTTTTGGGAAAGTGG
GGGGTTACTCTGTAACCAGTAACAGGGGAACTTGAAGGCAGCCACTTGACACTAATGCTGTTGTCCTGAACATC
GGTCACTTGCATCTGGGGATGGTTTTGACAATTTCTGGTTCGGCAAATTAATGGAAATTGGCTTGCTGCTTGGC
GGGGCTGNCTCCACGGGCCCAGTGACAGCATAC

16510.1.edit

16510.2.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAAC AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGACAAGTCTACAGCTACCATCAGCGGCCTTAAAC CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCAGTAAGCCAATT TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAGTAACCACCACTCCCAAAAATGGGACCAGGA CCAACAAAAAACTAAAACTGCANGGTCCAGATCAAACAGAAAATGACTATTGAAGGCTTGCAGCCCACAGTGGAG TATGTGGGTTAATGCTCAGAATNCCAAGCGGAGAGAGACTCAGCCTCTGGTTCAGACT

Fig. 15UU



82/101 16511.1.edit

16511.2.edit

AGCGTGGTCGCGGCCGAGGTCTGTAGCTTCTGTGGGACTTCCACTGCTCAGGCGTCAGGCTCAGGTAGCTGCTG
GCCGCGTACTTGTTGTTGCTTTGNTTGGAGGGTGTGGTGGTCTCCACTCCCGCCTTGACGGGGCTGCTATCTGC
CTTCCAGGCCACTGTCACGGCTCCCGGGTAGAAGTCACTTATGAGACACACCAGTGTGGCCTTGTTGGCTTGAA
GCTCCTCAGAGGAGGGTGGGAACAGAGTGACCGAGGGGGCAGCCTTGGGCTGACCTAGGACGGTCAGCTTGGTC
CCTCCGCCGAACACCCCAATTGTTGTTGCCTGCATATGAGCTGCAGTAATAATCAGCCTCATCCTCAGCCTGGAG
CCCAGAGACNGTCAAGGGAGGCCCGTGTTTGCCAAGACTTGGAAGCCAGANAAGCGATCAGGGACCCCTGAGGG
CCGCTTTACNGACCTCAAAAAAATCATGAATTTGGGGGGGCCTTTGCCTGGGNGTTGGTNACCAGNAAAACA
AAATTTCATAAAGCACCAACGTCACTGCTGGTTTCCAGTGCANGAANATGGTGAACTGAANTGTCC

16512.1.edit

16512.2.edit

TCGAGCGGCCGCCGGGCAGGTCCATACAGGGCTGTTGCCCAGGCCCTAGAGGNCATTCCTTGTACCCTGATCC
AGAACTGTGGGACCAGCACCATCCGTCTACTTACCTCCCTTCGGGCCAAGCACACCCAGGAGAACTGTGAGACC
TGGGGTGTAAATGGNGAGACGGGTACTTTGGTGGACATGAAGGAACTGGGCATATGGGAGCCATTGGCTGNGAA
GCTGCANACTTATAAGACAGCAGTGGAGACGGCAGTTCTGCTACTGCGAATTGATGACATCGTTTCAGGCCACA
AAAAGAAAGGCGATGACCANAGCCGGCAAGGCGGGCTTCCTGATGCTGGACCTCGGCCGCCGACCACGCTT

Fig. 15VV



16514.1.edit

AGCGTGGTCGCGGCCGAGGTCCACTAGAGGTCTGTGTGCCATTGCCCAGGCAGAGTCTCTGCGTTACAAACTCC
TAGGAGGGCTTGCTGTGCGGAGGGCCTGCTATGGTGTGCTGCGGTTCATCATGGAGAGTGGGGCCAAAGGCTGC
GAGGTTGTGGTGTCTGGGAAACTCCGAGGACAGAGGGCTAAATCCATGAAGTTTGTGGATGGCCTGATGATCCA
CAGCGGAGACCCTGTTAACTACTACGTTGACACTGCTGTGCGCCACGTGTTGCTCANACAGGGTGTGCTGGGCA
TCAAGGTGAAGATCATGCTGCCCTGGGACCCANCTGGCAAAAAATGGCCCTTAAAAAACCCCTTGCCNTGACCACG
TGAACCATTTGTGNGAACCCCCAAGATGAANATACTTGCCCACCCCCCCATTC

16514.2.edit

16515.1.edit

16515.2.edit

TCGAGCGGCCGGGCAGGTCTGGGCCAGGGGCACCAACACGTCCTCTCACCAGGAAGCCCACGGGCTCC
TGTTTGACCTGGAGTTCCATTTTCACCAGGGGCACCAGGTTCACCCTTCACACCAGGAGCACCGGGCTGTCCCT
TCAATCCATCCAGACCATTGTGNCCCCTAATGCCTTTGAAGCCAGGAAGTCCAGGAGTTCCAGGGAAACCACGA
GCACCCTGTGGTCCAACAACTCCTCTCTCACCAGGTCGTCCGGGTTTTCCAGGGTGACCATCTTCACCAGCCTT
GCCAGGAGGCCAGACCTCGGCCGCGACCACGCT

Fig. 15WW



16516.1.edit

ANCGTGGTCGCGGCCGAGGTCCTCACCAGAGGTGNCACCTACAACATCATAGTGGAGGCACTGAAAGACCANCAGAGGCATAAGGTTCGGGAAGAGG

16516.2.edit

TCGAGCGGCCGCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGTCCACGGTAACAACCTCTTCCCGAACCTTATGCC
TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCNGNCCNGAACAAC
GCTTAAGCCCGNATTCTGCAGAATAATCCCATCACACTTGGCGGCCGCCTTCGANCATGCATCNTAAAAGGGGCC
CCAATTTCCCCCTTATAAGNGAANCCGTATTTNCCAATTTCACTGGNCCCGCCGNTTTTTACAAACGNCGGTGAA
CTGGGGGAAAAAACCCTGGCGGTTACCCAACTTTAATCGCCNTTGGCAGCACAATCCCCCCTTTTCGNCCANCNTG

16517.1.edit

ANCGNGGTCGCGGCCGANGTNTTTTTTCTTNTTTTTTT

16518.1.edit

AGCGTGGTCGCGGCCGAGGTCTGAGGTTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGT
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TACCGGGNGGTCAGCGTCCTCACCGTCCTGCACCAGAATTGGTTGAATGGCAAGGAGTACAAGNGCAAGGTTTC
CAACAAAGCCNTCCCAGCCCCCNTCGAAAAAACCATTTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGT
ACACCCTGCCCCCATCCCGGGAGGAAAAAGANCAANAACCNGGTTCAGCCTTAACTTGCTTGGTCNAANACCTTTT
TATCCCAACGNACTTCCCCCNTGGAANTGGGAAAAAACCAATGGGCCAANCCGAAAAACAATTACAANAACCCC

16518.2.edit

Fig. 15XX



16519.1.edit

AGCGTGGTCGCGGACGANGTCCTGTCAGAGTGGNACTGGTAGAAGTTCCANGAACCCTGAACTGTAAGGGTTCT TCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGNGNCCTGGAATGGGGCCCATGANATGGTTGC

16519.2.edit

16520.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCCAAGTT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGGTNCCCTGGTACTGGGTTACAGANTAACCACCACTCCCAAAAATGGACCAGGA
ACCACAAAAACTTAAACTGCAGGGTCCAGATCAAAACAGAAATGACTATTGAANGCTTGCAGCCCACAGTGGGA
GTATGNGGGTAGTGNCTATGCTTCAGAATCCAAGCGGAAAAANGTCAAGCCTTNTGGGTTCAA

16520.2.edit

TCGAGCGGCCGCCGGGCAGGTCCTTGCAGCTCTGCAGTGTCTTCTTCACCATCAGGTGCAGGGAATAGCTCAT GGATTCCATCCTCAGGGCTCGAGTAGGTCACCCTGTACCTGGAAACTTGCCCCTGTGGGCTTTCCCAAGCAATT TTGATGGAATCGACATCCACATCAGTGAATGCCAGTCCTTTAGGGCGATCAATGTTGGTTACTGCAGNCTGAAC CAGAGGCTGACTCTCTCCGCTTGGATTCTGAGCATAGACACTAACCACATACTCCACTGTGGGCTGCAANCCTT CAATAANNCATTTCTGTTTGATCTGGACC

16521.2.edit

TCGAGCGGCCGCCCGGGCAGGTCTGGTGGGGTCCTGGCACACGCACATGGGGGNGTTGNTCTNATCCAGCTGCC CAGCCCCCATTGGCGAGTTTGAGAAGGTGTGCAGCAATGACAACAANACCTTCGACTCTTCCTGCCACTTCTTT GCCACAAAGTGCACCCTGGAGGGCACCAAGAAGGGCCACAAGCTCCACCTGGACTACATCGGGCCTTGCAAATA CATCCCCCCTTGCCTGGACTCTGAGCTGACCGAATTCCCCCTTGCGCATGCGGGACTGGCTCAAGAACCGTCCT GGCACCCTTGTATGANAGGGATGAAGACACNACCC

Fig. 15YY



16522.1.edit

16522.2.edit

TCGAGCGGCCGCCCGGGCAGGTTTGGAAGGGGGATGCGGGGGAAGAGAGACTGACGGTCCCCCAGGAGTTC AGGTGCTGGGCACGGTGGGCATGTTGTGAGTTTTGTCACAAGATTTGGGCTCAACTCTCTTGTCCACCTTGGTGT TGCTGGGCTTGTGATCTACGTTGCAGGTGTAGGTCTGGGNGCCGAAGTTGCTGGAGGGCACGGTCACCACGCTG CTGAGGGAGTAGAGTCCTGAGGACTGTANGACAGACCTCGGCCGNGACCACGCTAAGCCGAATTCTGCAGATAT CCATCACACTGGCGGCCGCTCCGAGCATGCATTTTAGAGG

16523.1.edit

AGCGTGGNCGCGGACGANGACAACAACCCC

16523.2.edit

TCGAGCGGCCGCCCGGGCAGGNCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTTGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGNACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCT

16524.1.edit

AGCGTGGTCGCGGCCGAGGTCCAGCCTGGAGATAANGGTGAAGGTGGTGCCCCCGGACTTCCAGGTATAGCTGG ACCTCGTGGTAGCCCTGGTGAGAGAGGTGAAACTGGCCCTCCAGGACCTGCTGTTTCCCTGGTGCTCCTGGAC AGAATGGTGAACCTGGNGGTAAAGGAGAAAGAGGGGCTCCGGNTGANAAAGGTGAAGGAGGCCCTCCTGNATTG GCAGGGGCCCCANGACTTAGAGGTGGAGCTGGCCCCCCTGGCCCCGAAGGAGGAAAGGGTGCTGCTGGTCCTCC TGGGCCACCTGG

Fig. 15ZZ



87/101 16524.2.edit

TCGAGCGGCCGGGCAGGTCTGGGCCAGGAGGACCAATAGGACCAGTAGGACCCCTTGGGCCATCTTTCCC
TGGGACACCATCAGCACCTGGACCGCCTGGTTCACCCTTGTCACCCTTTTGGACCAGGACTTCCAAGACCTCCTC
TTTCTCCAGGCATTCCTTGCAGACCAGGAGTACCANCAGCACCAGGTGGCCCAGGAGGACCAGCAGCACCCTTT
CCTCCTTCGGGACCAGGGGGACCAGCTCCACCTCTAAGTCCTGGGGCCCCTGCCAATCCAGGAGGGCCTCCTTC
ACCTTTCTCACCCGGAGCCCCTCTTTCT

16526.1.edit

TCGAGCGGCCGGCCGGGCAGGTCCACCGGGATATTCGGGGGGTCTGGCAGGAATGGGAGGCATCCAGAACGAGAA GGAGACCATGCAAAGCCTGAACGACCGCCTGGCCTCTTACCTGGACAGAGTGAGGAGCCTGGAGACCGACAACC GGAGGCTGGAGAGCAAAATCCGGGAGCACTTGGAGAAGAAGGGACCCCAGGTCAGAGACTGGAGCCATTACTTC AAGATCATCGAGGACCTGAGGGCTCANATCTTCGCAAATACTGCNGACAATGCCCG

16526.2.edit

ATGCGNGGTCGCGGCCGANGACCANCTCTGGCTCATACTTGACTCTAAAGNCNTCACCAGNANTTACGGNCATT GCCAATCTGCAGAACGATGCGGGCATTGTCCGCANTATTTGCGAAGATCTGAGCCCTCAGGNCCTCGATGATCT TGAAGTAANGGCTCCAGTCTCTGACCTGGGGTCCCTTCTTCTCCAAGTGCTCCCGGATTTTGCTCCCAGCCTC CGGTTCTCGGTCTCCAAGNCTTCTCACTCTGTCCAGGAAAAGAGGCCAGGCGGNCGATCAGGGCTTTTGCATGG ACT

16527.1.edit

16527.2.edit

TCGAGCGGCCCGGGCAGGTCTGCCAACACCAAGATTGGCCCCCGCCGCATCCACACAGTTNGTGTGCGGGG AGGTAACAAGAAATACCGTGCCCTGAGGNTGGACGNGGGGGAATTTCTCCTGGGGCTCAGAGTGTTGTACTCGTA AAACAAGGATCATCGATGTTGTCTACAATGCATCTAATAACGAGCTGGTTCGTACCAAGACCCTGGTGAAGAAT TGCATCGTGCTCATNGACAGCACACCGTACCGACAGTGGGTACCGAAGTCCCACTATGCNCCT

Fig. 15AAA



16528.1.edit

TCGAGCGGCCGCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGCCCTGAAG

16528.2.edit

AGCGTGNTCNCGGCCGAGGATGGGGAAGCTCGNCTGTCTTTTTCCTTCCAATCAGGGGCTNNNTCTTCTGATTA
TTCTTCAGGGCAANGACATAAATTGTATATTCGGNTCCCGGTTCCAGNCCAGTAATAGTAGCCTCTGTGACACC
AGGGCGGGCCGAGGGACCACTTCTCTGGGAGGAGACCCAGGCTTCTCATACTTGATGATGAAGCCGGTAATCC
TGGCACGTGGGCGGCCGCTGCCATGATACCACCAANGAATTGGGTGTGGTGGACCTGCCCGGGCGGCCGCTCGAAA
ANCCGAATTCNTGCAAGAATATCCATCACACTTGGGCGGGCCGNTCGAACCATGCATCNTAAAAGGGCCCCAAT
TTCCCCCCTATTAGGNGAAGCCNCATTTAACAAATTCCACTTGG

16529.1.edit

TCGAGCGGCCGCCCGGGCAGGTCTCGCGGTCGCACTGGTGATGCTGGTCCTGTTGGTCCCCCCGGCCCTCCTGG ACCTCCTGGTCCCCCTGGTCCTCCCAGCGCTGGTTTCGACTTCAGCTTCCTGCCCCAGCCACCTCAAGAGAAAGG CTCACGATGGTGGCCGCTACTACCGGGCTGATGATGCCAATGTGGTTCGTGACCGTGACCTCGAGGTGGACACC ACCCTCAAGAGCCTTGAGCCAGCAGAATCGAAAACATTCGGAACCCAAGAAGGGCAAGCCCGCAAAGAAACCCC GCCCGCACCTGGCCGNGAACCTCCAAGAANGTGCCCACNTCTTGACTGGGAAAAAAAAAGGGAAAANTACTTGGAA TTGGAC

16529.2.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA CTGGGCTGAGTGGGGTACACCGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAAGTGGCACATCTTGAGGTCACGGCAGGGT GCGGGCGGGGTTCTTGCGGGCTGCCCTTCTGGGCTCCCGGAATGTTCTNNGAACTTGCTGG

Fig. 15BBB



16530.1.edit

16530.2.edit

16531.1.edit

TCGAGCGGCCGCCCGGGCAGGTGTTTCAGAGGTTCCAAGGTCCACTGTGGAGGTCCCAGGAGTGCTGGTGG GCACAGAGGTCCGATGGGTGAAACCATTGACATAGAGACTGTTCCTGTCCAGGGTGTAGGGGCCCAGCTCTTTG ATGCCATTGGCCAGTTGGCTCAGCTCCCAGTACAGCCGCTCTCTGTTGAGTCCAGGGCTTTTGGGGTCAAGATG ATGGATGCAGATGGCATCCACTCCAGTGGCTGCTCCATCCTTCTCGGACCTGAGAGAGGTCAGTCTGCAGCCAG AGTACAGAGGGCCAACACTGGTGTTCTTTGAATA

16531.2.edit

AGCGTGGTCGCGGCCGAGGTCTGTACTGGGAGCTAAGCAAACTGACCAATGACATTGAAGAGCTGGGCCCCTAC ACCCTGGACAGGAACAGTCTCTATGTCAATGGTTTCACCCATCAGAGCTCTGTGNCCACCACCAGCACTCCTGG GACCTCCACAGTGGATTTCAGAACCTCAGGGACTCCATCCTCCTCCTGCAGCCCCACAATTATGGCTGCTGGCC CTCTCCTGGTACCATTCACCCTCAACTTCACCATCACCAACCTGCAGTATGGGGAGGACATGGGTCACCCTGNC TCCAGGAAGTTCAACACCACA

16532.1.edit

Fig. 15CCC

SUBSTITUTE SHEET (RULE 26)



90/101 **01** 16558.3.edit

AGCGTGGTCGCGGCCGAGGTGAGCCACAGGTGACCGGGGCTGAAGCTGGGGCTGCTGGNCCTGCTGGTCCTG

02 16558.4.edit

03 16535.1.edit

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04 16535.2.edit

AGCGNGGTCGCGGCCGAGGTCCAGCTCTGTCTCATACTTGACTCTAAAGTCATCAGCAGCAAGACGGGCATTGT CAATCTGCAGAACGATGCGGGCATTGTCCGCAGTATTTGCGAAGATCTGAGCCCTCAGGTCCTCGATGATCTTG AAGTAATGGCTCCAGGCTCCTGACCTGGGGTCCCTTCTTCTCCAAGTGCTCCCGGATTTTGCTCTCCAGGCCTCCG GTTCTCGGTCTCCAGGCTCCTCACTCTGTCCAGGTAAGAAGGCCCAGGCGGTCGTTCAGGCTTTGCATGGTCTC CTTCTCGTTCTGGATGCCTCCCATTCCTGCCAGACCC

05_16536.1.edit

Fig. 15DDD

SUBSTITUTE SHEET (RULE 26)



91/101 07 16537.1.edit

08_16537.2.edit

Fig. 15EEE

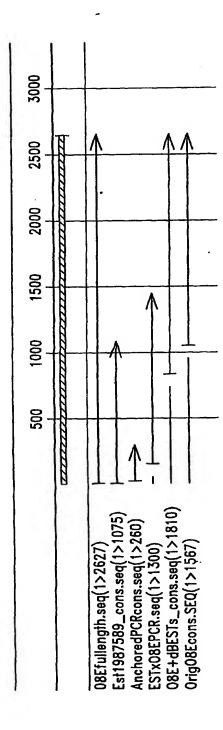


Fig. 16



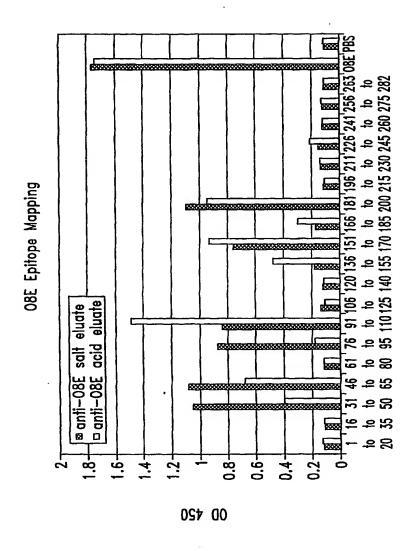
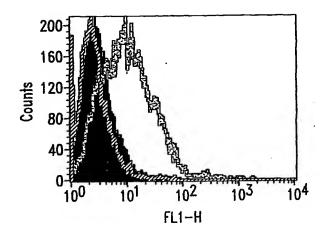


Fig. 17

OBE Surface Expression



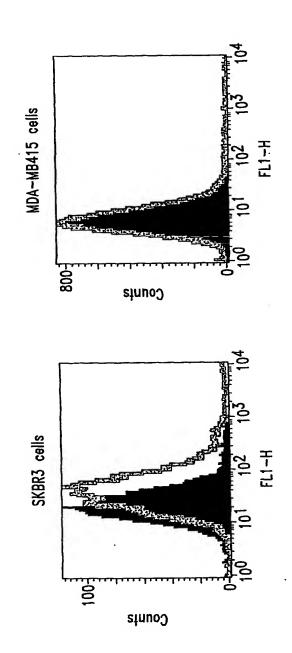
B305D/HEK stained with anti-08E antibody

08E/HEK stained with anti-08E antibody

08E/HEK stained with an irrelevant antibody

Fig. 18

Surface expression of OBE

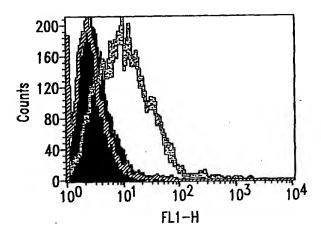


Black; irrelevant antibody Light gray; anti-08E antibody

Fig. 19



O8E Surface Expression



- B305D/HEK stained with anti-08E antibody
- O8E/HEK stained with anti-08E antibody
- 08E/HEK stained with an irrelevant antibody

Fig. 20

MDA-MB415 cells Surface expression of 08E 800-Strano SKBR3 cells 100-Counts

Black; Irrelevant antibody Light Grey; Anti-08E antibody

Fig. 21

O8E expression in HEK293 Cells (probed with anti-08E rabbit polyclonal sera #2333L)

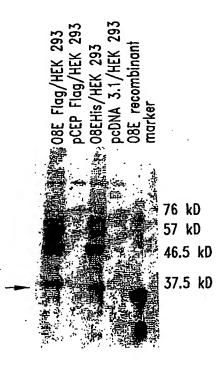


Fig. 22

08E Rabbits 01212000



99/101

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Fig. 23

Date: 1/21/99



100/101

affi-pure 08E #2576L 739.87A&B

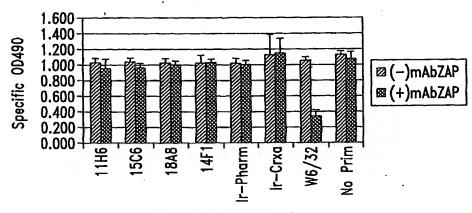
me O8E poly affinity pure α – O8E poly affinity pure α – O8E (2576L), 1/1 pss. me 08E poly affinity pure α – O8E (2576K); 2/8/2000 ncentration affinity pure α – O8E (2576K); 2/8/2000 1.1000 1; 1.10000 1; 1.10000 1; 1.1000 1; 1.10000 1; 1.1000 1; 1.1000 1; 1.1000 1; 1.1000 1; 1.1000 1; 1.1	000 08E polyclon affinity PBS #705, p15C #705, p15C 0.15 0.11 0.14 0.10 0.14 0.10 2.74 2.71 2.72 2.68 2.73 2.70 2.69 2.60 2.69 2.60 2.64 2.54 2.46 2.39 2.46 2.39	000 08E polyclonal affinity PBS #705, p150 affinity 0.15 0.15 0.14 0.10 0.09 0.14 0.10 0.10 0.10 0.10 0.10 0.10 0.10	000 OBE polyclonal affinity PBS #705, p150 1:1000 1:2000 1:4000 1:8000 0.15 0.11 0.09 0.08 0.14 0.10 0.09 0.08 0.14 0.10 0.09 0.08 2.74 2.71 2.63 2.49 2.72 2.68 2.64 2.47 2.73 2.70 2.63 2.48 2.69 2.60 2.50 2.21 2.59 2.48 2.38 2.21 2.54 2.54 2.44 2.21 2.56 2.56 2.56 2.56 2.56 2.57 2.56 2.56 2.57 2.57 2.68 2.54 2.77 2.68 2.54 2.77 2.68 2.54 2.77 2.68 2.54 2.77 2.68 2.54 2.77 2.68 2.54 2.77 2.68 2.54 2.77 2.68 2.54 2.77 2.68 2.54 2.77 2.68 2.54 2.77 2.68 2.50 2.77 2.70 2.7	000 OBE polyclonal affinity PBS #705, p150 1.7mg/m 1.1000 1:2000 1:4000 1:8000 1: 0.15 0.11 0.09 0.08 0.14 0.10 0.09 0.08 0.14 2.71 2.63 2.49 2.72 2.68 2.64 2.47 2.72 2.68 2.64 2.47 2.73 2.70 2.63 2.48 2.69 2.60 2.50 2.21 2.59 2.48 2.38 2.21 2.54 2.54 2.44 2.21 2.56 2.56 2.56 2.66 2.56 2.57 2.67 2.58 2.68 2.68 2.77 2.68 2.64 2.47 2.77 2.68 2.64 2.47 2.77 2.68 2.64 2.47 2.77 2.68 2.64 2.47 2.77 2.68 2.64 2.47 2.77 2.68 2.64 2.47 2.77 2.68 2.64 2.47 2.77 2.68 2.60 2.50 2.21 2.59 2.60 2.50 2.21 2.59 2.60 2.50 2.21 2.56 2.56 2.50 2.34 2.56 2.56 2.56 2.51 2.56 2.56 2.56 2.51 2.56 2.56 2.56 2.51	000 08E polyclonal affinity PBS #705, p150 1:1000 1:2000 1:4000 1:16000 1:15000 1:2000 1:4000 1:4000 1:16000	000 OBE polyclonal affinity PBS #705, p150 1:1000 1:2000 1:4000 1:8000 1:16000 1:32000 0.15 0.11 0.09 0.08 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.07 0.14 0.10 0.09 0.08 0.07 0.07 2.74 2.71 2.63 2.49 2.29 1.87 2.72 2.68 2.64 2.47 2.26 1.93 2.73 2.70 2.63 2.48 2.27 1.90 2.69 2.60 2.50 2.21 1.83 1.34 2.59 2.48 2.38 2.21 1.83 1.34 2.54 2.54 2.44 2.21 1.83 1.34 2.46 2.39 2.40 2.34 2.08 1.73 2.55 2.66 2.50 2.21 1.83 1.34 2.56 2.50 2.51 2.68 1.33 2.66 2.50 2.21 1.83 1.34 2.57 2.68 2.60 2.50 2.21 1.83 1.34 2.59 2.60 2.50 2.21 1.83 1.34 2.59 2.60 2.50 2.21 1.83 1.34 2.55 2.66 2.50 2.21 1.83 1.34 2.56 2.56 2.50 2.21 1.83 1.34 2.57 2.68 2.60 2.50 2.21 1.83 1.34 2.59 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34	000 OBE polyclonal affinity PBS #705, p150 1:1000 1:2000 1:4000 1:8000 1:16000 1:32000 0.15 0.11 0.09 0.08 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.07 0.14 0.10 0.09 0.08 0.07 0.07 2.74 2.71 2.63 2.49 2.29 1.87 2.72 2.68 2.64 2.47 2.26 1.93 2.73 2.70 2.63 2.48 2.27 1.90 2.69 2.60 2.50 2.21 1.83 1.34 2.59 2.48 2.38 2.21 1.83 1.34 2.54 2.54 2.44 2.21 1.83 1.34 2.46 2.39 2.40 2.34 2.08 1.73 2.55 2.66 2.50 2.21 1.83 1.34 2.56 2.50 2.51 2.68 1.33 2.66 2.50 2.21 1.83 1.34 2.57 2.68 2.60 2.50 2.21 1.83 1.34 2.59 2.60 2.50 2.21 1.83 1.34 2.59 2.60 2.50 2.21 1.83 1.34 2.55 2.66 2.50 2.21 1.83 1.34 2.56 2.56 2.50 2.21 1.83 1.34 2.57 2.68 2.60 2.50 2.21 1.83 1.34 2.59 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34 2.50 2.60 2.50 2.21 1.83 1.34	000 08E polyclonal affinity PBS #705, p150 affinity PBS #705, p150 1:1000 1:2000 1:4000 1:8000 1:16000 1:22000 1:28000 1:272 2.74 2.71 2.63 2.49 2.29 1.87 1.39 0.07 2.72 2.68 2.64 2.47 2.26 1.93 1.42 0.94 2.73 2.70 2.63 2.48 2.21 1.83 1.34 0.99 0.64 2.59 2.48 2.38 2.21 1.83 1.34 0.99 0.64 2.59 2.48 2.38 2.21 1.83 1.34 1.00 0.65 2.46 2.39 2.40 2.34 2.08 1.73 1.29 0.81 2.45 2.59 2.40 2.34 2.08 1.73 1.30 0.82 2.45 2.55 2.46 2.56 2.45 2.45 2.14 1.76 1.30 0.82	000 08E polyclonal affinity PBS #705, p150 739.87B 1.7mg/ml 1.7mg/ml 1.7mg/ml 1.7mg/ml 1.7mg/ml 1.1000 1:2000 1:4000 1:16000 1:32000 1:50000 1:50000 1:5000 1:5000 1:5000 1:2000 1:4000 1:2000 1:4000 1:20000 1:2000 1:2000 1:2000 1:2000 1:2000 1:2000 1:2000 1:2000 1:20000000000	000 08E polyclonal 576L, 1/11/2000 affinity PBS #705, p150 1.7mg/ml 3mg
E poly affin affin affin affin 1705, 1 7 705, 1 7 705, 1 7 705, 1 7 705, 1 7 705, 1 7 705, 1 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	E polyclon affinity PBS 7705, p150 0.15 0.11 0.10 0.15 0.11 0.10 0.14 0.10 0.14 0.10 0.14 0.10 0.14 0.10 0.14 0.10 0.14 0.10 0.14 0.10 0.16 0.16 0.16 0.16 0.16 0.16 0.16	E polyclonal affinity PBS 705, p150 1:4000 0.15 0.11 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.10 0.09 0.14 0.14 0.14 0.14 0.14 0.14 0.14 0.14	E polyclonal affinity PBS 705, p150 739.87E 1.7mg/ 3.mg 7.05, p150 1.4000 1.8000 0.15 0.11 0.09 0.08 0.14 0.10 0.09 0.08 0.14 0.10 0.09 0.08 0.14 0.10 0.09 0.08 0.14 0.10 0.09 0.08 0.14 0.10 0.09 0.08 0.14 0.17 0.14 0.10 0.09 0.08 0.14 0.17 0.14 0.10 0.09 0.08 0.14 0.17 0.14 0.10 0.09 0.08 0.14 0.17 0.14 0.10 0.14 0.14 0.14 0.14 0.14 0.14	E polyclonal affinity PBS 705, p150 739.87E 1.7mg/ 3.mg 7.05, p150 1.4000 1.8000 0.15 0.11 0.09 0.08 0.14 0.10 0.09 0.08 0.14 0.10 0.09 0.08 0.14 0.10 0.09 0.08 0.14 0.10 0.09 0.08 0.14 0.10 0.09 0.08 0.14 0.17 0.14 0.10 0.09 0.08 0.14 0.17 0.14 0.10 0.09 0.08 0.14 0.17 0.14 0.10 0.09 0.08 0.14 0.17 0.14 0.10 0.14 0.14 0.14 0.14 0.14 0.14	E polyclonal L, 1/11/2000 affinity PBS 705, p150 739.87B 1.7mg/ml 3mg 0.15 0.11 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 2.74 2.71 2.63 2.49 2.29 2.72 2.68 2.64 2.47 2.26 2.73 2.70 2.63 2.48 2.27 2.69 2.60 2.50 2.21 1.83 2.59 2.48 2.38 2.21 1.83 2.54 2.54 2.44 2.21 1.83 2.56 2.66 2.56 2.51 2.45 2.57 2.68 2.46 2.37 2.47 2.59 2.48 2.38 2.21 1.83 2.59 2.48 2.38 2.21 1.83 2.59 2.48 2.38 2.21 1.83 2.54 2.54 2.44 2.21 1.83	E polyclonal L, 1/11/2000 affinity PBS 705, p150 7739.87B 1.7mg/ml 3mg 0.15 0.11 0.09 0.08 0.07 0.07 0.14 0.10 0.09 0.08 0.07 0.07 0.14 0.10 0.09 0.08 0.07 0.07 2.74 2.71 2.63 2.49 2.29 1.87 2.72 2.68 2.64 2.47 2.26 1.93 2.73 2.70 2.63 2.48 2.27 1.90 2.69 2.60 2.50 2.21 1.83 1.34 2.59 2.48 2.38 2.21 1.83 1.34 2.54 2.54 2.44 2.21 1.83 1.34 2.55 2.48 2.36 2.21 1.83 1.34 2.56 2.56 2.57 2.58 1.33 2.57 2.68 2.58 2.51 1.83 1.34 2.59 2.48 2.38 2.21 1.83 1.34 2.59 2.48 2.38 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.56 2.56 2.57 2.44 2.21 1.83 1.34 2.57 2.68 2.60 2.57 2.44 2.21 1.83 1.34 2.58 2.48 2.38 2.40 2.34 2.08 1.73 2.59 2.48 2.58 2.48 2.54 2.08 1.73 2.50 2.50 2.51 2.55 2.50 2.50 2.51 2.55 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0.55 0.55 0.55 0.55 0.55 0.58 0.58 0.58	E polyclonal affinity PBS 705, p150 Aritibody Dilutions 1.7mg/ml 1.7mg/ml 1.7mg/ml 2.14 2.71 2.63 2.49 2.29 1.87 1.39 0.92 0.57 0.33 0.20 2.72 2.68 2.64 2.47 2.26 1.93 1.42 0.94 0.57 0.34 0.21 2.73 2.70 2.63 2.48 2.27 1.90 1.41 0.93 0.54 0.21 2.59 2.48 2.38 2.21 1.83 1.34 0.99 0.64 0.38 0.22 0.15 2.54 2.54 2.54 2.21 1.83 1.34 0.99 0.64 0.38 0.22 0.15 2.55 2.48 2.34 2.21 1.83 1.34 0.99 0.64 0.38 0.22 0.15 2.55 2.56 2.56 2.56 2.51 1.83 1.34 1.00 0.65 0.37 0.32 0.15 2.56 2.56 2.56 2.57 1.83 1.34 1.00 0.65 0.37 0.29 0.19 2.56 2.56 2.56 2.51 1.83 1.34 1.00 0.65 0.37 0.29 0.19 2.57 2.58 2.48 2.21 1.83 1.34 1.00 0.65 0.37 0.24 0.21 2.58 2.58 2.58 2.51 1.83 1.34 1.00 0.65 0.37 0.32 0.15 2.59 2.48 2.38 2.21 1.83 1.34 1.00 0.65 0.37 0.29 0.19
	11/200 11/200 11/200 111 0 110 0 10 0		739.87E 1.7mg/ 3mg 3mg 0.08 0.08 0.08 1.249 2.21 2.21 3.2.21 4.2.21 4.2.21 4.2.21 4.2.21 2.34	739.87E 1.7mg/ 3mg 3mg 0.08 0.08 0.08 1.249 2.21 2.21 3.2.21 4.2.21 4.2.21 4.2.21 4.2.21 2.34	739.87B 1.7mg/ml 3mg 0 1:8000 1:16000 0 0.08 0.07 0 0.08 0.07 1 2.49 2.29 1 2.49 2.29 2.49 2.29 3 2.21 1.83 3 2.21 1.83 4 2.21 1.83 2 2.21 1.83 3 2.21 1.83 4 2.21 1.83 5 2.45 2.14	739.87B 1.7mg/ml 3mg 0 18000 1:16000 1:32000 0.08 0.07 0.07 0.08 0.07 0.07 1 2.49 2.29 1.87 1 2.47 2.26 1.93 2 2.48 2.27 1.90 2 2.1 1.83 1.34 3 2.21 1.83 1.34 4 2.21 1.83 1.34 1 2.45 2.14 1.76	739.87B 1.7mg/ml 3mg 0 18000 1:16000 1:32000 0.08 0.08 0.07 0.08 0.07 0.07 1 2.49 2.29 1.87 1 2.47 2.26 1.93 2 2.48 2.27 1.90 2 2.1 1.83 1.34 3 2.21 1.83 1.34 4 2.21 1.83 1.34 1 2.45 2.14 1.76	739.87B 1.7mg/ml 3mg 0.08 0.08 0.07 0.07 0.07 0.08 0.07 0.07 0.07 1.249 2.29 1.87 1.39 0.92 1.248 2.27 1.90 1.41 0.93 2.21 1.83 1.34 0.99 0.64 3 2.21 1.83 1.34 1.00 0.63 4 2.21 1.83 1.34 1.00 0.63 2.34 2.08 1.73 1.29 0.81 2.45 2.14 1.76 1.30 0.82	739.87B 1.7mg/ml 3mg 0.18000 1:16000 1:32000 1:64000 1:128000 1:256000 0.08 0.07 0.07 0.07 0.07 0.08 0.07 0.07 0.07 0.07 1 2.49 2.29 1.87 1.39 0.92 0.57 2.49 2.21 1.83 1.34 0.99 0.64 0.38 2.21 1.83 1.34 0.99 0.65 0.37 4 2.21 1.83 1.34 1.00 0.65 0.37 2.24 2.08 1.73 1.29 0.81 0.49 2.34 2.08 1.73 1.30 0.82 0.87	Antibody Dilutions Antibody 0.37 0.37 0.37 Antibody Dilutions A

Fig. 24



Anti-08E mAb Binding to 08E Amino Acids 61-80 Induces Ligand Internalization

Hek Internalization of OBE mAbs



Primary Ab (50ng/well)

Hek/O8E Internalization of O8E mAbs

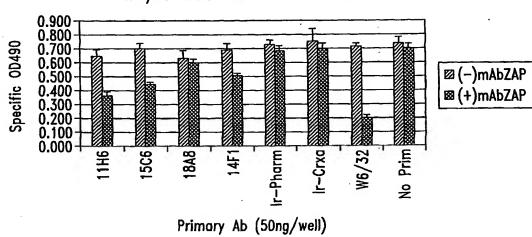


Fig. 25

1

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tatctaaaat ctcacttgta ggagaaacca caggcaccag agctgccact ggtgctggca 180
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geoegeaggg etteaagggg teccatagee titigggeee geagggeate aaggaetegg 180
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<212> DNA
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<222> 481
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caatcaggaa gactttttcc ttcttcaaga agtgaagggt ttccagagta tagctacact 180
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<210> 9
<211> 531
<212> DNA
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<222> 528
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<211> 541
<212> DNA
<213> Homo sapiens
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atgaagctag caagtgatga tatgataaaa taaacgtgga ggaaataaaa acacaagact 180
tggcataaga tatatccact tttgatatta aacttgtgaa gcatattctt cgacaaattg 240
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<210> 14
<211> 131
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 126
<223> n = A, T, C or G
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tgccgntgcc g
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<211> 692
<212> DNA
<213> Homo sapiens
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tcagtatttt ttttatttct atgcaaaagt atgccttcaa actgcttaaa tgatatatga 180
tatgatacac aaaccagttt tcaaatagta aagccagtca tcttgcaatt gtaagaaata 240
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5



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<212> DNA
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tgatggtttc ataaggcttt teecectttt geteageact teteetteet geegeeatgt 180
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tccaaagg
<210> 17
<211> 531
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 518, 528
<223> n = A, T, C or G
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<210> 18
<211> 1041
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 544
<223> n = A, T, C or G
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448
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<211> 411
<212> DNA
<213> Homo sapiens
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<210> 22
<211> 896
<212> DNA
<213> Homo sapiens
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<222> 230, 320
<223> n = A, T, C or G
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<210> 23
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<210> 24
<211> 531
<212> DNA
<213> Homo sapiens
<220>
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<222> 472, 494
\langle 223 \rangle n = A, T, C \text{ or } G
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<210> 25
<211> 471
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 377
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ggttctcact tcagtatgct atctcgacac cttcctaatc tccagacgca caaagaaaat 360
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<210> 26
<211> 541
<212> DNA
<213> Homo sapiens
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cttccatagc agcaacagat gctttggggc taaaaggcat gtcctctgac cttgcaggtg 300
gtggattttg ctcttttaca acatgtacat ccttactggg ctgtgctgtc acagggatgt 360
ccttgctgga ctgttctgct atggggatat cttcgttgga ctgttcttca tgcttaattg 420
cagtattagc atccacatca gacagcctgg tataaccaga gttggtggtt actgattgta 480
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g
<210> 27
<211> 461
<212> DNA
<213> Homo sapiens
<220>
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<221> misc_feature
<222> 367
<223> n = A,T,C or G
<400> 27
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cetcaattca agcagtcatt gteettgett teaaaagtet gtgtgtgett catggaaggt 240
atatgtttgt tgccttaatt tgaattgtgg ccaggaaggg tctggagatc taaattcaga 300
gtaagaaaac ctgagctaga actcaggcat ttctcttaca gaacttggct tgcagggtag 360
aatgaangga aagaaactta gaagctcaac aagctgaaga taatcccatc aggcatttcc 420
cataggeett geaactetgt teactgagag atgttateet g
<210> 28
<211> 541
<212> DNA
<213> Homo sapiens
<400> 28
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aactagacaa gtgtgttaag agtgataagt aaaatgcacg tggagacaag tgcatcccca 180
gateteaggg acctecect geetgteace tggggagtga gaggacagga tagtgcatgt 240
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aagacgctgc taattgactg ccacttcgca actcaggggc ggctgcattt tagtaatggg 420
tcaaatgatt cacttttat gatgetteec aaggtgeett ggettetett eccaactgac 480
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<210> 29
 <211> 411
 <212> DNA
 <213> Homo sapiens
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 tgtcatccat attctgggac tcaggcggga actttctgga atattgccag ggagcatggc 180
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 tacattacct ctgttcacaa ctcattgccc agcaccagtc acaaggcccc accaaatacc 300
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 <210> 30
 <211> 511
 <212> DNA
 <213> Homo sapiens
 <400> 30
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 acagttctgc atggctgaag aggcctcagg aaacttacag tcatggtgga aggcaaagga 180
 ggagcaaggc atgtcttaca tgtcagtagg agagagagcg agagcaggag aacctgccac 240
 ttataaacca ttcagatctc ataactccct atcatgagaa aaacatggag gaaaccaccc 300
 tcatgatcca atcacctccc gccaggtccc tccctcgaca cgtggggatt ataattcagg 360
 attagaggga cacagagaca aaccatatca tcattcatga gaaatccacc ctcatagtcc 420
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 <210> 31
 <211> 827
 <212> DNA
 <213> Homo sapiens
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 tcacagtgtc cactcaaggg cagcttggtc ctcttgtcct gcagaggcag gctggtgtga 180
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 agatacaagc teettgtgge tggaaaaaca eeeetetget gataaagete agggggeact 360
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 tecetetygt geteceaegt etgtteetea ecetecatet etgggageag etgeaeetga 480
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 tggcttacaa agtagagttg gcccagtttc cttccacctg aggggagcac tctgactcct 600
 aacagtette ettgeeetge cateatetgg ggtggetgge tgteaagaaa ggeegggeat 660
 getttetaaa cacagecaca ggaggettgt agggeatett ceaggtgggg aaacagtett 720
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 <210> 32
 <211> 291
 <212> DNA
 <213> Homo sapiens
 <400> 32.
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 ccacagcagt cagttggtca ggccctgctg tagaaggtca cttggctcca ttgcctgctt 180
 ccaaccaatg ggcaggagag aaggcettta tttetegeec acceattete etgtaccage 240
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  <210> 33
  <211> 491
  <212> DNA
  <213> Homo sapiens
  <400> 33
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  gaacatcact cacttcccct acttgatcta caaggccaac gccgagagcc cagaccagga 120
  ttecaaacae actgeacgag aatattgtgg atcegetgte aggtaagtgt eegteactga 180
  cccaracgct gttacgtggc acatgactgt acagtgccac gtaacagcac tgtacttttc 240
  tcccatgaac agttacctgc catgtatcta catgattcag aacattttga acagttaatt 300
  ctgacacttg aataatccca tcaaaaaccg taaaatcact ttgatgtttg taacgacaac 360
  atagçatcac tttacgacag aatcatctgg aaaaacagaa caacgaatac atacatctta 420
  aaaaatgctg gggtgggcca ggcacagctt cacgcctgta atcccagcac tttgggaggc 480
  ttaagcgggt g
  <210> 34
  <211> 521
  <212> DNA
  <213> Homo sapiens
  <220>
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12



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<221> misc feature
<222> 453, 476, 487
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<400> 34
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tggatggaaa tgaaaattac ccgtgtcttg tggatgcaga cggtgatgtg atttccttcc 180
caccaataac caacagtgag aagacaaagg ttaagaaaac gacttctgat ttgtttttgg 240
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actgaagecg atgeagtete tggacaaett ecagatecea caacgaatee cagtgetgga 420
aaggacgggc cetteettet ggtggtggaa cangteeegg tggtggatet tggaanggaa 480
cctgaangtg gtgtaccccg tccaaggccg accttggcca c
<210> 35
<211> 161
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 18
<223> n = A, T, C or G
<400> 35
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cgccgcgctg ccgaccgyca gcatgctgcc gagagtgggc tgccccgcgc tgccgctgcc 120
geogeogeog etgetgeege tgetgeeget getgetgetg e
<210> 36
<211> 341
<212> DNA
<213> Homo sapiens
<400> 36
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aaaaaaccaa aattategee aagatteage aaaggggaca gggageteea geeegagage 120
ctattattag cagtgaggag cagaagcagc tgatgctgta ctatcacaga agacaagagg 180
agctcaagag attggaagaa aatgatgatg atgcctattt aaactcacca tgggcggata 240
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 gttcaccage tgatgacact tccaaagaga ttagetcace t
 <210> 37
 <211> 521
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 516
 <223> n = A, T, C or G
 <400> 37
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 tgttgttgtt gatgatgatg atgatgatga taatatttt ctatccccag tgcacaactg 180
 cttgaaccta ttagataatc aatacatgtt tcttgaactg agatcaattt ccccatgttg 240
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```
tetgaetgat gaageeetae attttettet agaggagatg acatttgage aagatettaa 300
agaaaatcag atgeetteac etgaceactg ettggtgate ceatggeact ttgtacatet 360
ctccattagc tetcatetca ecageccate attattgtat gtgetgeett etgaagettg 420
cagetggeta ccatcmggta gaataaaaat catcetttca taaaatagtg acceteettt 480
tttatttgca tttcccaaag ccaagcaccg tggganggta g
<210> 38
<211> 461
<212> DNA
<213> Homo sapiens
<400> 38
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<210> 39.
<211> 769
<212> DNA
<213> Homo sapiens
<400> 39
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gatgtegeet tttettette ttgettttte tgatgttetg etcageatgt tetgggtget 180
teteatetge atcatteett teagatgetg tagettette eteetette tgeeteettt 240
tettttttt ttttttgggg ggcttgctct ctgactgcag ttgaggggcc ccagggtcct 300
ggeetttgag acgagecagg aaggeetget eetgggeete taggegagea agettggeet 360
teattgtgat eccaagaegg geageettgt gtgetgtteg ecceteaeag gettggagea 420
geateteate agteagaate tttggggaet tggacecetg gttgtegtea teaetgeage 480
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geteatteca ecagtggttt gtgaacteet tggcagggtc atgteetace ecatgagtgt 720
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<210> 40
<211> 292
<212> DNA
<213> Homo sapiens
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aaactcgaaa aatgagcaag tctggtggga gtggaggaag ggctatacta taaatccaag 120
tgggeeteet gatettaaca agecatgete attatacaca tetetgaact ggacatacca 180
cetttacgca ggaaacaggg cttggaactt ctaagggaaa ttaacatgca ccacccacat 240
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<210> 41
<211> 406
 <212> DNA
<213> Homo sapiens
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tgatggaaaa agcagacagg aactggtggg aggtcaagtg gggaagttgg tgaatgtgga 180
ataacttacc tttgtgctcc acttaaacca gatgtgttgc agctttcctg acatgcaagg 240
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gatataatct gccaggctat gtgacagtag gaaggaatgg tttcccctaa caagcccaat 360
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<210> 42
<211> 381
<212> DNA
<213> Homo sapiens
<400> 42
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tegeaccage caageettaa etgeetgeet gaecetgaac cagaacceag etgaactgee 240
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<210> 43
<211> 451
<212> DNA
<213> Homo sapiens
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ctatatteet ggetetgtgt tteegagaet gettttaate ceaacttete tacatttaga 180
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<210> 44
<211> 521
 <212> DNA
 <213> Homo sapiens
 <400> 44
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 cagaccataa atcaacttct tgctgaaatg gatggtttta aacccaatga aggagttatc 300
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 ttttgacatg caagttacag ttccaaggcc agatgtaaaa ggtcgaacag aaattttgaa 420
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 <210> 45
 <211> 585
 <212> DNA
 <213> Homo sapiens
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aggttgatct ttgccggaaa gcagctggaa gatggdcgca ccctgtctga ctacaacatc 240
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<210> 46
<211> 481
<212> DNA
<213> Homo sapiens
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<210> 47
<211> 461
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 128
<223> n = A, T, C or G
<400> 47
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<210> 48
<211> 571
<212> DNA
<213> Homo sapiens
<400> 48
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```
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<210> 49
<211> 511
<212> DNA
<213> Homo sapiens
<400> 49
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<210> 50
<211> 561
<212> DNA
<213> Homo sapiens
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 <212> DNA
 <213> Homo sapiens
 <400> 51
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<212> DNA
<213> Homo sapiens
<400> 75
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ggaagacctg ggggaaaaca ccatggtttt atccaccctg agatctttga acaacttcat 180
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<210> 76
<211> 330
<212> DNA
<213> Homo sapiens
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<222> 288
<223> n = A, T, C or G
<400> 76
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tcagcctgca gccagagtac agagggccaa cactggtgtt cttgaacaag ggccttagca 180
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<211> 361
<212> DNA
<213> Homo sapiens
<400> 77
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cagecaccag agtggatget gtetgeacce ategteetga ecceaaaage cetggaetgg 180
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<210> 78
<211> 356
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<213> Homo sapiens
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<221> misc feature
<222> 7, 346, 350, 353
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<210> 79
<211> 226
<212> DNA
<213> Homo sapiens
<400> 79
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catttaatac acctaacgta tcgaacatca tagcttggcc caggttatct catatgtgct 180
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<210> 80
<211> 444
<212> DNA
<213> Homo sapiens
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<221> misc feature
<222> 23
<223> n. = A, T, C or G
<400> 80
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gsmgmssgag gmwggwgtyy cwgaggttcy rarrtccact gtggaggtcc caggagtgct 180
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<211> 310
<212> DNA
<213> Homo sapiens
<400> 81
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<211> 571
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 202
<223> n = A, T, C or G
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<210> 83
<211> 551
<212> DNA
<213> Homo sapiens
<400> 83
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cgagcttcac tttccaaget aggggatgtc tatgtcaatg atgettttgg cactgctcac 180
agagcccaca getecatggt aggagtcaat etgccacaga aggetggtgg gtttttgatg 240
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<212> DNA
<213> Homo sapiens
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<211> 561
<212> DNA
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<212> DNA
<213> Homo sapiens
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cacageteaa gtaagttagg aaaetgagee aagtataeae agaataegaa gtggeaaaae 180
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<210> 87
<211> 594
<212> DNA
<213> Homo sapiens
<400> 87
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aatagccaat ggctggttat attttcagaa aacatgatta gactaattca ttaatggtgg 180
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 <210> 88
 <211> 557
 <212> DNA
 <213> Homo sapiens
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<210> 89
<211> 561
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 544, 551
<223> n = A, T, C or G
<400> 89
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<210> 90
<211> 561
<212> DNA
<213> Homo sapiens
<400> 90
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<210> 91
<211> 541
<212> DNA
<213> Homo sapiens
<220>
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<221> misc_feature
<222> 480, 491
<223> n = A, T, C or G
<400> 91
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<210> 92
<211> 551
<212> DNA
<213> Homo sapiens
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<211> 531
<212> DNA
<213> Homo sapiens
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                                                                 531
<210> 94
<211> 531
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 517
<223> n = A, T, C or G
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<210> 95
<211> 605
<212> DNA
<213> Homo sapiens
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<211> 531
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<213> Homo sapiens
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<211> 1017
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 963, 995, 1001, 1008, 1010
<223> n = A, T, C or G
<400> 97
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<400> 114
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caccgagget gagageaaca tgaacgacet cgtctctgag tatcaagcag taccaggatg 180
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<210> 122
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<212> DNA
<213> Homo sapiens
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<212> DNA
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<222> 166, 202, 222, 225
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<211> 521
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<221> misc_feature
<222> 284, 412, 513
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<212> DNA
<213> Homo sapiens
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<220>
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<222> 277
<223> n = A, T, C or G
<400> 125
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tgtggcatct gcagctggga agagagaggc cggggaggtg ccgagctcgg tgctggtetc 180
tttccaaata taaatacgtg tgtcagaact ggaaaatcct ccagcaccca ccacccaagc 240
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<210> 126
<211> 521
<212> DNA
<213> Homo sapiens
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<222> 353, 399, 455
<223> n = A, T, C or G
<400> 126
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geecageetg tateaggeae teaagttgtg cagggacaga tecagacaet tgccaccaat 240
gctcaacaga ttacacagac agaggtccag caaggacagc agcagttcaa gccagttcac 300
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ccageccatg ttcatccagt caagecaace agecettena egggeaggee ecceaggtga 420
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<211> 351
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taaatatact aatagctaag tcatttgcca gccaggtccc ggtgaacagt agagaacaag 180
gagettgeta agaattaatt ttgetgtttt teaccecatt caaacagage tgecetgtte 240
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catectaagg geacttgeea getettatee ggacagteaa geactgttgt tggacaacag 480
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<213> Homo sapiens
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cttggtgaat acagtctcct tccagaggtc gggggtcagg tagctgtagg tcttagaaat 180
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<211> 341
<212> DNA
<213> Homo sapiens
<400> 131
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<211> 844
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 37
<223> n = A, T, C or G
<400> 132
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gccatgtgga acatgagggg ctgcctgagc ccctcaccct gagatggggc aaggaggagc 180
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tggtcatcct tggagctgtg atggcttttg tgatgaagag gaggagaaac acaggtggaa 300
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ccctgcactg ccctgtgttc ccttccacag ccaaccttgc tgctccagcc aaacattggt 600
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gagaataata atttgaatgt gggtggctgg agagatggct cagcgctgac tgctcttcca 720
aaggteetga gttcaaatee cagcaaceae atggtggete acaaceatet gtaatgggat 780
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<211> 601
<212> DNA
<213> Homo sapiens
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cageegeteg teagacteca geageeaaga tggtgaagea gategagage aagaetgett 180
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<210> 134
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<212> DNA
<213> Homo sapiens
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teceteacag cacegittta tatatageag agaataatga agagattget agictagatg 360
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tgtactaaaa cccaacataa tttcttacta tgtgagtgag gatctgaagg ataagaaagg 480
agacattete ttggatgaaa attgetgtgt agaagteett geetgacaaa agatggaaag 540
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aaatgccttt t
<210> 138
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<212> DNA
<213> Homo sapiens
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<222> 490
<223> n = A, T, C or G
<400> 138
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tttcaaggan gcaggaaagc aattaagtgg tcaccttaac ataaggggga c
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<211> 521
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 517
<223> n = A, T, C or G
<400> 139
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<212> DNA
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<400> 140
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<212> DNA
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<211> 491
<212> DNA
<213> Homo sapiens
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<221> misc_feature
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<212> DNA
<213> Homo sapiens
<400> 143
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 ctacaaggcc agcagatccc taattetete tecaatcaag tgegetetee ecageetgte 180
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 <213> Homo sapiens
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45



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<210> 150
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 <212> DNA
 <213> Homo sapiens
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 <221> misc_feature
 <222> 457, 479
 <223> n = A, T, C or G
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 ggccagacag gaagtggcaa gacacatact atgggcggag acctctctgg gaaagcccag 240
 aatgcatcca aagggatcta tgccatggcc ttccgggacg tcttcttctg aagaatcaac 300
 cctgctaccg gaagttgggc ctggaagtct atgtgacatt cttcgagatc tacaatggga 360
 agetgtttga cetgetcaac aagaaggeca agettgegeg tgetggaaga eggeaagcaa 420
 caggtgcaag tggtggggc ttgcaggaac atctggntaa ctctgcttga tgatggcant 480
 caagatgatc gacatgggca gcgcctgcag a
 <210> 151
 <211> 566
 <212> DNA
 <213> Homo sapiens
 <400> 151
 tecegaatte aagegacaaa ttggawagtg aaatggaaga tgeetateat gaacateagg 60
 caaatetttt gegecaagat etgatgagae gacaggaaga attaagaege atggaagaae 120
 ttcacaatca agaaatgcag aaacgtaaag aaatgcaatt gaggcaagag gaggaacgac 180
 gtagaagaga ggaagagatg atgattegte aaegtgagat ggaagaacaa atgaggegee 240
 aaagagagga aagttacagc cgaatgggct acatggatcc acgggaaaga gacatgcgaa 300
 tgggtggcgg aggagcaatg aacatgggag atccctatgg ttcaggaggc cagaaatttc 360
  cacctetagg aggtggtggt ggcataggtt atgaagctaa tcctggcgtt ccaccagcaa 420
  ccatgagtgg ttccatgatg ggaagtgaca tgcgtactga gcgctttggg cagggaggtg 480
```

```
cggggcctgt gggtggacag ggtcctagag gaatggggcc tggaactcca gcaggatatg 540
                                                                  566
gtagagggag agaagagtac gaaggc
<210> 152
<211> 518
<212> DNA
<213> Homo sapiens
<400> 152
ttcgtgaaga ccctgactgg taagaccatc actctcgaag tggagcccga gtgacaccat 60
tgagaatgtc aaggcaaaga tccaagacaa ggaaggcatc cctcctgacc agcakaggtt 120
gatetttget gggaaacage tggaagatgg acgeaccetg tetgactaca acatecagaa 180
agagtccacc ctgcacctgg tgctccgtct cagaggtggg atgcaaatct tcgtgaagac 240
cctgactggt aagaccatca ccctcgaggt ggagcccagt gacaccatcg agaatgtcaa 300
ggcaaagatc caagataagg aaggcatccc tcctgatcag cagaggttga tctttgctgg 360
gaaacagetg gaagatggac gcaccetgte tgactacaac atccagaaag agtecactet 420
gcacttggtc ctgcgcttga gggggggtgt ctaagtttcc ccttttaagg tttcaacaaa 480
tttcattgca ctttcctttc aataaagttg ttgcattc
<210> 153
<211> 542
<212> DNA
<213> Homo sapiens
<400> 153
gegegggtge gtgggceact gggtgacega cttageetgg ccagaetete ageaeetgga 60
agegecega gagtgacage gtgaggetgg gagggaggae ttggettgag ettgttaaac 120
tetgetetga geeteettgt egeetgeatt tagatggete eegeaaagaa gggtggegag 180
aagaaaaagg gccgttctgc catcaacgaa gtggtaaccc gagaatacac catcaacatt 240
cacaagegca tecatggagt gggetteaag aagegtgeae etegggeaet caaagagatt 300
cggaaatttg ccatgaagga gatgggaact ccagatgtgc gcattgacac caggctcaac 360
aaagetgtet gggecaaagg aataaggaat gtgccatace gaateegtgt geggetgtee 420
agaaaacgta atgaggatga agattcacca aataagctat atactttggt tacctatgta 480
cctgttacca ctttcaaaaa tctacagaca gtcaatgtgg atgagaacta atcgctgatc 540
gt
<210> 154
<211> 411
<212> DNA
<213> Homo sapiens
<400> 154
aattetttat ttaaatcaac aaacteatet teeteaagee eeagaceatg gtaggeagee 60
ctecetetee ateceeteae eccaeceett agecacagtg aagggaatgg aaaatgagaa 120
gccacgaggg cccctgccag ggaaggctgc cccagatgtg tggtgagcac agtcagtgca 180
gctgtggctg gggcagcagc tgccacaggc tcctccctat aaattaagtt cctgcagcca 240
cagctgtggg agaagcatac ttgtagaagc aaggccagtc cagcatcaga aggcagaggc 300
agcatcagtg actcccagcc atggaatgaa cggaggacac agagctcaga gacagaacag 360
gccaggggga agaaggagag acagaatagg ccagggcatg gcggtgaggg a
<210> 155
<211> 421
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 173
```



```
<223> n = A, T, C or G
<400> 155
tgatgaatct gggtgggctg gcagtagccc gagatgatgg gctcttctct gggggatccca 60
actggttccc taagaaatcc aaggagaatc ctcggaactt ctcggataac cagctgcaag 120
agggcaagaa cgtgatcggg ttacagatgg gcaccaaccg cggggcgtct cangcaggca 180
tgactggcta cgggatgcca cgccagatcc tctgatccca ccccaggcct tgcccctgcc 240
ctcccacgaa tggttaatat atatgtagat atatatttta gcagtgacat tcccagagag 300
ccccagaget etcaagetee tttetgteag ggtggggggt tcaageetgt cctgteaeet 360
ctgaagtgcc tgctggcatc ctctccccca tgcttactaa tacattccct tccccatagc 420
<210> 156
<211> 670
<212> DNA
<213> Homo sapiens
<400> 156
ageggagete ceteceetgg tggetacaac ceacacacge caggetcagg categageag 60
aactccagcg actgggtaac cactgacatt caggtgaagg tgcgggacac ctacctggat 120
acacaggtgg tgggacagac aggtgtcatc cgcagtgtca cgggggggcat gtgctctgtg 180
tacctgaagg acagtgagaa ggttgtcagc atttccagtg agcacctgga gcctatcacc 240
eccaccaaga acaacaaggt gaaagtgate etgggegagg ategggaage caegggegte 300
ctactgagca ttgatggtga ggatggcatt gtccgtatgg accttgatga gcagctcaag 360
atcetcaace teegetteet ggggaagete etggaageet gaageaggea gggeeggtgg 420
acttcgtcgg atgaagagtg atcetectte ettecetgge eettggetgt gacacaagat 480
cetectgeag ggetaggegg attgttetgg atttectitt gttttteett ttaggtttee 540
atcttttccc tccctggtgc tcattggaat ctgagtagag tctgggggag ggtccccacc 600
tteetgtace teeteecac agettgettt tgttgtaceg tettteaata aaaagaaget 660
gtttggtcta
<210> 157
<211> 421
<212> DNA
<213> Homo sapiens
<400> 157
ggttcacagc actgctgctt gtgtgttgcc ggccaggaat tccaggctca caaggctatc 60
ttagcagctc gttctccggt ttttagtgcc atgtttgaac atgaaatgga ggagagcaaa 120
aagaatcgag ttgaaatcaa tgatgtggag cctgaagttt ttaaggaaat gatgtgcttc 180
atttacacgg ggaaggetee aaacetegae aaaatggetg atgatttget ggeagetget 240
gacaagtatg ccctggagcg cttaaaggtc atgtgtgagg atgccctctg cagtaacctg 300
 teegtggaga acgetgeaga aatteteate etggeegace teeacagtge agateagttg 360
 aaaactcagg cagtggattt catcaactat catgcttcgg atgtcttgga gacctcttgg 420
 <210> 158
 <211> 321
 <212> DNA
 <213> Homo sapiens
 <400> 158
 tegtagecat ttttetgett etttggagaa tgaegecaea etgaetgete attgtegttg 60
 gttccatgcc aattggtgaa atagaacctc atccggtagt ggagccggag ggacatcttg 120
 tcatcaacgg tgatggtgcg atttggagca taccagagct tggtgttete gccatacagg 180
 gcaaagaggt tgtgacaaag aggagagata cggcatgcct gtgcagccct gatgcacagt 240
 teetetgetg tgtactetee actgeecage eggagggget eeetgteega cagatagaag 300
                                                                    321
 atcacttcca cccctggctt g
```



```
<210> 159
<211> 596
<212> DNA
<213> Homo sapiens
<400> 159
tggcacactg ctcttaagaa actatgawga tctgagattt ttttgtgtat gtttttgact 60
cttttgagtg gtaatcatat gtgtctttat agatgtacat acctccttgc acaaatggag 120
gggaattcat tttcatcact gggagtgtcc ttagtgtata aaaaccatgc tggtatatgg 180
cttcaagttg taaaaatgaa agtgacttta aaagaaaata ggggatggtc caggatctcc 240
actgataaga ctgtttttaa gtaacttaag gacctttggg tctacaagta tatgtgaaaa 300
aaatgagact tactgggtga ggaaattcat tgtttaaaga tggtcgtgtg tgtgtgtgt 360
ttgaaattac tgkgtaaata tatgtytgat aatgatttgc tytttgvcma ctaaaattag 480
gvetgtataa gtwetaratg cmteeetggg kgttgatytt ccmagatatt gatgatamee 540
cttaaaattg taaccygcct ttttcccttt gctytcmatt aaagtctatt cmaaag
<210> 160
<211> 515
<212> DNA
<213> Homo sapiens
<400> 160
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cagtgtcaga ggcccgcgtt cagcccaaga atgtggattt tctctcccta ttgatcacag 120
tgggtgggtt tcttcagaaa agccccagag gcagggacca gtgagctcca aggttagaag 180
tggaactgga aggetteagt cacatgetge ttecaegett ceaggetggg cageaaggag 240
gagatgecca tgaegtgeca ggteteccca tetgaeacca gtgaagtetg gtaggaeage 300
agcegcaège etgeetetge caggaggeca atcatggtag geageattge agggteagag 360
gtetgagtee ggaataggag caggggcagg teeetgegga gaggcaette tggcetgaag 420
acagetecat tgageceetg cagtacaggy gtagtgeett ggaccaagee cacageetgg 480
taaggggcgc ctgccagggc cacggccagg aggca
<210> 161
<211> 936
<212> DNA
<213> Homo sapiens
<400> 161
taatttctta gtcgtttgga atccttaagc atgcaaaagc tttgaacaga agggttcaca 60
aaggaaccag ggttgtctta tggcatccag ttaagccaga gctgggaatg cctctgggtc 120
atccacatca ggagcagaag cacttgactt gtcggtcctg ctgccacggt ttgggcgccc 180
accaegecea egtecacete gtecteceet geegecaegt cetgggegge caaggtetee 240
aaaattgate tecagetgag acgttatate atttgetgge tteeggaaat gatggteeat 300
aaccgaatct tcagcatgag cctcttcact ctttgattta tgaagaacaa atcccttctt 360
 ccactgccca tcagcacctt catttggttt tcggatatta aattctactt ttgcccggtc 420
 cttattttga atagcettee acteateeaa agteatetet tttggaceet cetetttae 480
 ctcttcaact tcattctcct tattttcagt gtctgccact ggatgatgtt cttcaccttc 540
 aggtgtttcc tcagtcacat ttgattgatc caagtcagtt aattcgtctt tgacagttcc 600
 ccagttgtga gatccgctac ctccacgttt gtcctcgtgc ttcaggccag atctatcact 660
 tecactatge etateaaatt caegtttgee acgagaatea aateeatete eteggeeeat 720
 tecaegteca eggececete gacetettee aagaceacea egacetegaa taggteggte 780
 aataateggt ctateaactg aaaattegee teetteaece tittetteaa gtggettite 840
 gaatettegt teacgaggtg gtegeettte tggtetteta teaattattt teeetteace 900
                                                                  936
 ctgaagttgt tgatcaggtc ttcttccaac tcgtgc
```

```
<211> 950
<212> DNA
<213> Homo sapiens
<400> 162
aagcggatgg acctgagtca gccgaatcct, agccccttcc cttgggcctg ctgtggtgct 60
cgacatcagt gacagacgga agcagcagac catcaaggct acgggaggcc cggggcgctt 120
gcgaagatga agtttggctg cctctccttc cggcagcctt atgctggctt tgtcttaaat 180
ggaatcaaga ctgtggagac gcgctggcgt cctctgctga gcagccagcg gaactgtacc 240
ategeegtee acattgetea cagggactgg gaaggegatg cetgteggga getgetggtg 300
gagagactcg ggatgactcc tgctcagatt caggccttgc tcaggaaagg ggaaaagttt 360
ggtcgaggag tgatagcggg actcgttgac attggggaaa ctttgcaatg ccccgaagac 420
ttaactcccg atgaggttgt ggaactagaa aatcaagctg cactgaccaa cctgaagcag 480
aagtacctga ctgtgatttc aaaccccagg tggttactgg agcccatacc taggaaagga 540
ggcaaggatg tattccaggt agacatccca gagcacctga tccctttggg gcatgaagtg 600
tgacaagtgt gggctcctga aaggaatgtt ccrgagaaac cagctaaatc atggcacctt 660
caatttgcca tcgtgacgca gacctgtata aattaggtta aagatgaatt tccactgctt 720
tggagagtcc cacccactaa gcactgtgca tgtaaacagg ttcctttgct cagatgaagg 780
aagtaggggg tggggctttc cttgtgtgat gcctccttag gcacacaggc aatgtctcaa 840
gtactttgac cttagggtag aaggcaaagc tgccagtaaa tgtctcagca ttgctgctaa 900
ttttggtcct gctagtttct ggattgtaca aataaatgtg ttgtagatga
<210> 163
<211> 475
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 301, 317, 331, 458, 464, 470
<223> n = A, T, C or G
<400> 163
tegageggee geeegggeag gtgteggagt ceageaeggg aggegtggte ttgtagttgt 60
teteeggetg eccattgete teccaeteca eggegatgte getgggatag aageetttga 120
ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtgt 180
acacctgtgg ttctcggggc tgccctttgg ctttggagat ggttttctcg atgggggctg 240
ggagggettt gttggagace ttgcacttgt actecttgce attcaaccag teetggtgca 300
ngacggtgag gacgctnacc acacggtacg ngctggtgta ctgctcctcc cgcggctttg 360
tettggcatt atgcacetec acgccgteca cgtaccaatt gaacttgace teagggtett 420
 cgtggctcac gtccaccacc acgcatgtaa cctcaaanct cggncgcgan cacgc
 <210> 164
 <211> 476
 <212> DNA
 <213> Homo sapiens
 <400> 164
 agcgtggtcg cggccgaggt ctgaggttac atgcgtggtg gtggacgtga gccacgaaga 60
 ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120
 geogegggag gageagtaca acageacgta cegtgtggte agegteetea cegteetgca 180
 ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc 240
 ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtacac 300
 cctgcccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct gcctggtcaa 360
 aggettetat eccagegaca tegecegtgg agtgggagag caatgggeag eeggagaaca 420
 actacaagac cacgcctccc gtgctggact ccgacacctg ccgggcggcc gctcga
```



```
<211> 256
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 10, 37, 249
\langle 223 \rangle n = A, T, C or G
<400> 165
agegtggttn eggeegaggt eccaaccaag getgeancet ggatgecate aaagtettet 60
gcaacatgga gactggtgag acctgcgtgt accccactca gcccagtgtg gcccagaaga 120
actggtacat cagcaagaac cccaaggaca agaggcatgt ctggttcggc gagagcatga 180
cegatggatt ccagttcgag tatggcggcc agggctccga ccctgccgat gtggacctgc 240
ccgggcggnc gctcga
<210> 166
<211> 332
<212> DNA
<213> Homo sapiens
<400> 166
agegtggteg eggeegaggt caagaaceee geeegcaeet geegtgaeet caagatgtge 60
cactetgact ggaagagtgg agagtactgg attgacccca accaaggetg caacetggat 120
gecatcaaag tettetgeaa catggagaet ggtgagaeet gegtgtaeee caetcageee 180
agtgtggccc agaagaactg gtacatcagc aagaacccca aggacaagag gcatgtctgg 240
tteggegaga geatgacega tggattecag ttegagtatg geggeeaggg eteegaeeet 300
                                                                       332
gccgatgtgg acctgcccgg gcggccgctc ga
<210> 167
<211> 332
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 77, 109, 136, 184, 198
<223> n = A, T, C or G
<400> 167
tegageggte gecegggeag gtecacateg geagggtegg agecetggee gecatacteg 60
aactggaatc catcggncat gctctcgccg aaccagacat gcctcttgnc cttggggttc 120
ttgctgatgt accagntett ctgggccaca ctgggctgag tggggtacac gcaggtetca 180
ccantctcca tgttgcanaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240 atccagtact ctccactctt ccagacagag tggcacatct tgaggtcacg gcaggtgcgg 300
                                                                        332
gcggggttet tgacctcggt cgcgaccacg ct
<210> 168
<211> 276
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 72, 84
 <223> n = A, T, C or G
 <400> 168
```



```
tegageggee geeegggeag gteeteetea gageggtage tgttettatt geeeeggeag 60
cctccataga tnaagttatt gcangagttc ctctccacgt caaagtacca gcgtgggaag 120
gatgcacggc aaggcccagt gactgcgttg gcggtgcagt attcttcata gttgaacata 180
tegetggagt ggaetteaga atcetgeett etgggageae ttgggaeaga ggaateeget 240
qcattectqc tqqtqqacct cggccgcgac cacgct
<210> 169
<211> 276
<212> DNA
<213> Homo sapiens
<400> 169
agegtggteg eggeegaggt ceaceageag gaatgeageg gatteetetg teecaagtge 60
teccagaagg caggattetg aagaceacte cagegatatg tteaactatg aagaatactg 120
cacegecaac geagteactg ggeettgeeg tgeateette ceaegetggt actttgaegt 180
ggagaggaac teetgeaata actteateta tggaggetge eggggeaata agaacageta 240
ccqctctgag gaggacctgc ccgggcggcc gctcga
<210> 170
<211> 332
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 294
<223> n = A, T, C or G
<400> 170
tegageggee geeegggeag gtecacateg geagggtegg ageeetggee geeatacteg 60
aactggaatc catcggtcat gctctcgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagteteca tgttgcagaa gactttgatg gcatecaggt tgcageettg gttggggtca 240
atccagtact etecactett ecagecagaa tggeacatet tgaggteaeg geangtgegg 300
qeqqqttct tgacctcggc cgcgaccacg ct
<210> 171
<211> 333
<212> DNA
<213> Homo sapiens
<400> 171
agcgtggtcg cggccgaggt caagaaaccc cgcccgcacc tgccgtgacc tcaagatgtg 60
ccactctggc tggaagagtg gagagtactg gattgacccc aaccaaggct gcaacctgga 120
tgccatcaaa gtcttctgca acatggagac tggtgagacc tgcgtgtacc ccactcagcc 180
cagtgtggcc cagaagaact ggtacatcag caagaacccc aaggacaaga ggcatgtctg 240
gctcggcgag agcatgaccg atggattcca gttcgagtat ggcggccagg gctccgaccc 300
tgccgatgtg gacctgcccg ggcggccgct cga
<210> 172
<211> 527
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 46, \overline{1}25, 140, 148, 220, 229, 291, 388, 456
<223> n = A, T, C or G
```



```
<400> 172
agegtggteg eggeegaggt cetgteagag tggcactggt agaagnteea ggaaccetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctgnaatgg ggcccatgan atggttgnct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgn gggcggtgng gtccgcctaa 240
aaccatgtte etcaaagate atttgttgee caacactggg ttgetgacea naagtgeeag 300
gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctgntc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgctgtct ttttccttcc aatcangggc tcgctcttct gaatattctt 480
cagggcaatg acataaattg tatattcggt tcccggttcc aggccag
<210> 173
<211> 635
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 444, 453, 517, 540, 546, 551, 573, 593
<223> n = A, T, C or G
<400> 173
tegageggee gecegggeag gtecaceaea eccaatteet tgetggtate atggeageeg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagcccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agacceettt egteacceae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatett tgangaacat ggntttagge ggaccacace ggccacaacg 480
ggcaccccca taaggcatag gccaagaaca tacccgncga atgtaggaca agaagctctn 540
teteanacaa neateteatg ggeeceatte cangacaett etgagtaeat cantteatgg 600
catcctggtg gcactgataa aaacccttac agtta
<210> 174
<211> 572
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 457, 511, 520, 552, 568
<223> n = A, T, C \text{ or } G
<400> 174
agegtggteg egggegaggt cetgteagag tggcactggt agaagtteea ggaaccetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca gaagtgccag 300
gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgtctgtc tttttccttc caatcanggg ctcgctcttc tgattattct 480
tcagggcaat gacataaatt gtatattcgg ntcccgggtn cagccaataa taataaccct 540
ctqtqacacc anggcggggc cgaagganca ct
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```
<211> 372
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 247
<223> n = A, T, C or G
<400> 175
agegtggteg eggeegaggt ceteaceaga ggtaceacet acaacateat agtggaggea 60
ctgaaagacc agcagaggca taaggttcgg gaagaggttg ttaccgtggg caactctgtc 120
aacgaagget tgaaccaacc tacggatgac tegtgetttg accectacac agttteccat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttangct ttggaagtgg tcatttcaga tgtgattcat ctagatggtg ccatgacaat 300
ggtgtgaact acaagattgg agagaagtgg gaccgtcagg gagaaaatgg acctgeccgg 360
geggeegete ga
<210> 176
<211> 372
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 251
<223> n = A, T, C or G
<400> 176
tegageggee geeegggeag gteeatttte teeetgaegg teceaettet etecaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagectaag cactggcaca acagtttaaa geetgattea gacattegtt eccaeteate 180
tecaacggca taatgggaaa etgtgtaggg gtcaaagcac gagtcatecg taggttggtt 240
caageetteg ntgacagagt tgeccaeggt aacaacetet teeegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggta cctctggtga ggacctcggc 360
                                                                    372
cgcgaccacg ct
<210> 177
 <211> 269
<212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 94, 225
 <223> n = A, T, C or G
 <400> 177
 agcgtggccg cggccgaggt ccattggctg gaacggcatc aacttggaag ccagtgatcg 60
 teteageett ggtteteeag etaatggtga tggnggtete agtageatet gteacaegag 120
 cccttcttgg tgggctgaca ttctccagag tggtgacaac accctgagct ggtctgcttg 180
 tcaaagtgtc cttaagagca tagacactca cttcatattt ggcgnccacc ataagtcctg 240
 atacaaccac ggaatgacct gtcaggaac
 <210> 178
 <211> 529
 <212> DNA
 <213> Homo sapiens
```



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<400> 178
tegageggee geeegggeag gteeteagae egggttetga gtacacagte agtgtggttg 60
ccttgcacga tgatatggag agccagcccc tgattggaac ccagtccaca gctattcctg 120
caccaactga cetgaagtte actcaggtea cacccacaag cetgagegee cagtggacae 180
cacccaatgt tcagctcact ggatatcgag tgcgggtgac ccccaaggag aagaccggac 240
caatgaaaga aatcaacctt gctcctgaca gctcatccgt ggttgtatca ggacttatgg 300
cggccaccaa atatgaagtg agtgtctatg ctcttaagga cactttgaca agcagaccag 360
ctcagggtgt tgtcaccact ctggagaatg tcagcccacc aagaagggct cgtgtgacag 420
atgetactga gaccaccatc accattaget ggagaaccaa gactgagacg atcactgget 480
tccaagttga tgccgttcca gccaatggac ctcggccgcg accacgctt
<210> 179
<211> 454
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 64
<223> n = A, T, C or G
<400> 179
agcgtggtcg cggccgaggt ctggccgaac tgccagtgta cagggaagat gtacatgtta 60
tagntettet egaagteeeg ggeeageage teeaeggggt ggteteetge eteeaggege 120
ttotcattot catggatott ottoaccogo agottotgot totcagtcag aaggttgttg 180
tecteatece teteatacag ggtgaccagg acgttettga gecagteceg catgegeagg 240
gggaattcyg tcagctcaga gtccaggcaa ggggggatgt atttgcaagg cccgatgtag 300
tccaagtgga gcttgtggcc cttcttggtg ccctccaagg tgcactttgt ggcaaagaag 360
tggcaggaag agtcgaaggt cttgttgtca ttgctgcaca ccttctcaaa ctcgccaatg 420
                                                                    454
ggggctgggc agacctgccc gggcggccgc tcga
<210> 180
<211> 454
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 55, \overline{2}99, 317, 332, 342, 348
<223> n = A, T, C \text{ or } G
<400> 180
tegageggee geeegggeag gtetgeeeag eeceeattgg egagtttgag aaggngtgea 60
gcaatgacaa caagacette gactetteet gccacttett tgccacaaag tgcaccetgg 120
agggcaccaa gaagggccac aagctccacc tggactacat cgggccttgc aaatacatcc 180
ccccttgcct ggactctgag ctgaccgaat tccccctgcg catgcgggac tggctcaaga 240
acgtectggt caccetgtat gagagggatg aggacaacaa cettetgact gagaagcana 300
agctgcgggt gaagaanatc catgagaatg anaagcgcct gnaggcanga gaccaccccg 360
tggagctgct ggcccgggac ttcgagaaga actataacat gtacatcttc cctgtacact 420
ggcagttcgg ccagacctcg gccgcgacca cgct
<210> 181
<211> 102
<212> DNA
<213> Homo sapiens
<220>
```



```
<221> misc feature
\langle 222 \rangle 8, 47, 60, 67
<223> n = A, T, C or G
<400> 181
agegtggntg eggacgaege ceacaaagee attgtatgta gttttantte agetgeaaan 60
aataccncca gcatccacct tactaaccag catatgcaga ca
<210> 182
<211> 337
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 169, 195, 253, 314
<223> n = A, T, C \text{ or } G
<400> 182
tcgagcggtc gcccgggcag gtctgggcgg atagcaccgg gcatattttg gaatggatga 60
ggtctggcac cctgagcagc ccagcgagga cttggtctta gttgagcaat ttggctagga 120
ggatagtatg cagcacggtt ctgagtctgt gggatagctg ccatgaagna acctgaagga 180
ggcgctggct ggtangggtt gattacaggg ctgggaacag ctcgtacact tgccattctc 240
tgcatatact ggntagtgag gcgagcctgg cgctcttctt tgcgctgagc taaagctaca 300
                                                                   337 ·
tacaatggct ttqnqgacct cggccgcgac cacgctt
<210> 183
<211> 374
<212> DNA
<213> Homo sapiens
<400> 183
tcgagcggcc gcccgggcag gtccattttc tccctgacgg tcccacttct ctccaatctt 60
gtagttcaca ccattgtcat gacaccatct agatgaatca catctgaaat gaccacttcc 120
aaageetaag caetggeaca acagtttaaa geetgattea gacattegtt cecaeteate 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caagcetteg ttgacagaag ttgcccacgg taacaaccte ttcccgaacc ttatgcetet 300
gctggtcttt caagtgcctc cactatgatg ttgtaggtgg cacctctggt gaggacctcg 360
gccgcgacca cgct
<210> 184
<211> 375
<212> DNA ·
<213> Homo sapiens
<220>
<221> misc feature
<222> 30, 174, 248, 285, 306, 332, 345, 368
<223> n = A, T, C or G
<400> 184
agegtggttt geggeegagg teeteacean aggtgeeace tacaacatea tagtggagge 60
actgaaagac cagcagaggc ataaggttcg ggaagaggtt gttaccgtgg gcaactctgt 120
caacgaaggc ttgaaccaac ctacggatga ctcgtgcttt gacccctaca cagnttccca 180
ttatgccgtt ggagatgagt gggaacgaat gtctgaatca ggctttaaac tgttgtgcca 240
gtgcttangc tttggaagtg gtcatttcag atgtgattca tctanatggt gtcatgacaa 300
tggtgngaac tacaagattg gagagaagtg gnaccgtcag ggganaaaat ggacctgccc 360
                                                                    375
gggcggcncg ctcga
```



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<210> 185
<211> 148
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 28, 36, 86
<223> n = A, T, C or G
<400> 185
agegtggteg eggeegaggt etggettnet geteangtga ttateetgaa eeateeagge 60
caaataagcg ccggctatgc ccctgnattg gattgccaca cggctcacat tgcatgcaag 120
tttgctgagc tgaaggaaaa gattgatc
<210> 186
<211> 397
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 78
\langle 223 \rangle n = A, T, C or G
<400> 186
tegageggee geeegggeag gtecaattga aacaaacagt tetgagaceg ttettecace 60
actgattaag agtggggngg cgggtattag ggataatatt catttagcct tctgagcttt 120
ctgggcagac ttggtgacct tgccagctcc agcagccttc tggtccactg ctttgatgac 180
acceaeegea aetgtetgte teatateaeg aacageaaag egaeeeaaag gtggatagte 240
tgagaagete teaacacaca tgggettgee aggaaceata teaacaatgg geageateae 300
cagacttcaa gaatttaagg gccatcttcc agctttttac cagaacggcg atcaatcttt 360
                                                                    397
tccttcagct cagcaaactt gcatgcaatg tgagccg
<210> 187
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 145, 286, 363, 365, 425, 433, 452, 462, 471, 512, 514, 534,
536, 540, 565, 583
\langle 223 \rangle n = A, T, C or G
tegageggee geeegggeag gteeagaggg etgtgetgaa gtttgetget geeactggag 60
ccactccaat tgctggccgc ttcactcctg gaaccttcac taaccagatc caggcagcct 120
teegggagee acggettett gtggntactg accccaggge tgaccaccag cetetcacgg 180
aggeatetta tgttaaceta cetaceattg cgctgtgtaa cacagattet cetetgcgct 240
atgtggacat tgccatccca tgcaacaaca agggagctca ctcagngggg tttgatgtgg 300
tggatgctgg ctcgggaagt tctgcgcatg cgtggcacca tttcccgtga acacccatgg 360
gangneatge etgatetgga ettetacaga gateetgaag agattgaaaa agaagaacag 420
gctgnttgct ganaaagcaa gtgaccaagg angaaatttc angggtgaaa nggactgctc 480
ccgctcctga attcactgct actcaacctg angntgcaga ctggtcttga aggngnacan 540
gggccctctg ggcctattta agcancttcg gtcgcgaaca cgnt
```



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<210> 188
<211> 579
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 7, 136, 486
<223> n = A, T, C or G
<400> 188
agegtgngtc geggeegagg tgctgaatag geacagaggg cacetgtaca cettcagace 60
agtetgeaac etcaggetga gtageagtga acteaggage gggageagte catteaccet 120
gaaatteete ettggneact geetteteag eageageetg etettettt teaatetett 180
caggatetet gtagaagtac agateaggea tgacetecea tgggtgttca egggaaatgg 240
tgccacgcat gcgcagaact tcccgagcca gcatccacca catcaaaccc actgagtgag 300
ctcccttgtt gttgcatggg atgggcaatg tccacatagc gcagaggaga atctgtgtta 360
cacagegeaa tggtaggtag gttaacataa gatgeeteeg egagaagetg gtggteagee 420
ctggggtcaa gtaaccacaa gaagccgtgg ctcccggaag gctgcctgga tctggttagt 480
gaaggnteca ggagtgaage ggecaacaat tggagtgget teagtggeaa geageaaact 540
tcagcacaag ccctctggac ctgcccggcg gccgctcga
<210> 189
<211> 374
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 41, \overline{2}80, 314, 330, 350, 353
<223> n = A, T, C or G
<400> 189
tegageggee geeegggeag gteeattte teeetgaegg neceaettet etecaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaageetaag cactggcaca acagtttaaa geetgattea gacattegtt eccacteate 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgeccaeggt aacaaceten teecegaace ttatgeetet 300
gctgggcttt cagngcctcc actatgatgn tgtagggggg cacctctggn gangacetcg 360
                                                                    374
geegegaeca eget
<210> 190
<211> 373
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 247, 304, 306, 332, 337
<223> n = A, T, C or G
<400> 190
agcgtggtcg cggccgaggt cctcaccaga ggtgccacct acaacatcat agtggaggca 60
ctgaaagacc agcagaggca taaggctcgg gaagaggttg ttaccgtggg caactctgtc 120
aacgaagget tgaaccaacc tacggatgac tegtgetttg acccetacac agttteccat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttangct ttggaagtgg gtcatttcag atgtgattca tctagatggt gccatgacaa 300
tggngngaac tacaagattg gagagaagtg gnaccgncag ggagaaaatg gacctgcccg 360
```



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373
ggcggccgct cga
<210> 191
<211> 354
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 218, 299, 306, 326, 333, 337, 341
<223> n = A, T, C or G
<400> 191
agegtggteg eggeegaggt ecacategge agggteggag ecetggeege catactegaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
gctgatgtac cagttettet gggccacact gggctgagtg gggtacacgc aggtetcacc 180
agtetecatg ttgcagaaga etttgatgge atccaggntg caacettggt tggggtcaat 240
ccagtactct ccactcttcc agccagagtg gcacatcttg aggtcacggc aggtgcggnc 300
gggggntttt geggetgeee tetggnette ggntgtnete natetgetgg etca
<210> 192
<211> 587
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 276
<223> n = A,T,C or G
<400> 192
tegageggee geeegggeag gtetegeggt egeactggtg atgetggtee tgttggteec 60
cceggecete etggacetee tggcccccet ggtcctccca gcgctggttt cgacttcage 120
tteetgeece agecacetea agagaagget cacgatggtg geogetaeta eegggetgat 180
gatgecaatg tggttegtga ecgtgacete gaggtggaca ceacceteaa gageetgage 240
cagcagateg agaacateeg gageecagag ggeagnegea agaaceeege eegeacetge 300
cgtgacctca agatgtgcca ctctgactgg aagagtggag agtactggat tgaccccaac 360
caagetgeaa cetggatgee atcaaagtet tetgeaacat ggagaetggt gagaeetgeg 420
tgtaccccae tcagcccagt gtggcccaaa agaactggta catcagcaag aaccccaagg 480
acaagaagca tgtctggttc ggcgagaaca tgaccgatgg attccagttc gagtatggcg 540
ggcagggctc cgaccctgcc gatggggacc ttggccgcga acacgct
<210> 193
<211> 98
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9, 33, 58, 71, 90
<223> n = A, T, C or G
<400> 193
agegtggnng eggeegaggt ataaatatee agneeatate eteceteeae aegetganag 60
atgaagetgt neaaagatet cagggtggan aaaaccat
<210> 194
<211> 240
```



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<212> DNA
<213> Homo sapiens
tcgagcggcc gcccgggcag gtccttcaga cttggactgt gtcacactgc caggcttcca 60
gggctccaac ttgcagacgg cctgttgtgg gacagtctct gtaatcgcga aagcaaccat 120
ggaagacctg ggggaaaaca ccatggtttt atccaccctg agatctttga acaacttcat 180
ctctcagcgt gcggagggag gctctggact ggatatttct acctcggccg cgaccacgct 240
<210> 195
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 22, 37, 39, 105, 268, 276, 302, 323, 331, 335, 347, 351,
371, 378
<223> n = A, T, C or G
<400> 195
cgagcggcg accgggcagg tncagactcc aatccanana accatcaagc cagatgtcag 60
aagctacacc atcacaggtt tacaaccagg cactgactac aaganctacc tgcacacctt 120
gaatgacaat geteggaget eeeetgtggt categaegee tecaetgeea ttgatgeace 180
atccaacetg cgtttcctgg ccaccacacc caattccttg ctggtatcat ggcagecgcc 240
acgtgccagg attaccggta catcatcnag tatganaagc ctgggcctcc tcccagagaa 300
gnggtccctc ggccccgccc tgntgtccca naggntacta ttactgngcc ngcaaccggc 360
aaccqatatc nattttgnca ttggccttca acaataatta
<210> 196
<211> 494
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 19, 83, 168, 252, 271, 292, 430
<223> n = A, T, C or G
<400> 196
agegtggttc geggeegang teetgteaga gtggeactgg tagaagttcc aggaaccetg 60
aactgtaagg gttcttcatc agngccaaca ggatgacatg aaatgatgta ctcagaagtg 120
tcctggaatg gggcccatga gatggttgtc tgagagagag cttcttgncc tgtcttttc 180
cttccaatca ggggctcgct cttctgatta ttcttcaggg caatgacata aattgtatat 240
tcgggtcccg gntccaggcc agtaatagta ncctctgtga caccagggcg gngccgaggg 300
accacttctc tgggaggaga cccaggettc tcatacttga tgatgtaacc ggtaatcctg 360
gcacgtggcg gctgccatga taccagcaag gaattggggt gtggtggcca ggaaacgcag 420
gttggatggn gcatcaatgg cagtggaggc cgtcgatgac cacaggggga gctccgacat 480
                                                                   494
tgtcattcaa ggtg
<210> 197
<211> 118
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
```



```
<222> 8, 71, 96
\langle 223 \rangle n = A, T, C or G
<400> 197
agegtggneg eggeegaggt geagegeggg etgtgeeace ttetgetete tgeecaacga 60
taaggagggt neetgeeccc aggagaacat taactnteec eageteggee tetgeegg
<210> 198
<211> 403
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 41, 53, 98, 195, 350
<223> n = A, T, C or G
<400> 198
tcgagcggcc gcccgggcag gttttttttg ctgaaagtgg ntactttatt ggntgggaaa 60
gggagaaget gtggteagee caagagggaa tacagagnee egaaaaaggg gagggeaggt 120
gggctggaac cagacgcagg gccaggcaga aactttctct cctcactgct cagcctggtg 180
gtggctggag ctcanaaatt gggagtgaca caggacacct tcccacagcc attgcggcgg 240
catttcatct ggccaggaca ctggctgtcc acctggcact ggtcccgaca gaagcccgag 300
ctggggaaag ttaatgttca cctgggggca ggaaccctcc ttatcattgn gcagagagca 360
                                                                     403
gaaggtggca cagcccgcgc tgcacctcgg ccgcgaccac gct
<210> 199
<211> 167
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 92, 107
<223> n = A, T, C or G
<400> 199
tegageggee gecegggeag gtecaccata agtectgata caaccaegga tgagetgtea 60
ggagcaaggt tgatttcttt cattggtccg gncttctcct tgggggncac ccgcactcga 120
tatccagtga gctgaacatt gggtggcgtc cactgggcgc tcaggct
                                                                      167
<210> 200
<211> 252
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 210, 226, 227, 230, 236
\langle 223 \rangle n = A, T, C or G
<400> 200
togagoggtt cgcccgggca ggtccaccac acccaattcc ttgctggtat catggcagcc 60
gccacgtgcc aggattaccg gctacatcat caagtatgag aagcctgggt ctcctcccag 120
agaageggte ceteggeece geeetggtgt cacagagget actattactg geetggaace 180
gggaaccgaa tatacaattt atgtcattgn cctgaagaat aatcannaan agcgancccc 240
tgattggaag ga
```

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<210> 201
<211> 91
<212> DNA
<213> Homo sapiens
<400> 201
tttttttt ttttttt ttttttt t
<210> 202
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 9, 354
<223> n = A, T, C or G
<400> 202
tcgagcggnc gcccgggcag gtctgccaac accaagattg gccccgccg catccacaca 60
gtccgtgtgc ggggaggtaa caagaaatac cgtgccctga ggttggacgt ggggaatttc 120
tectgggget cagagtgttg tactegtaaa acaaggatea tegatgttgt etacaatgea 180
tctaataacg agctggttcg taccaagacc ctggtgaaga attgcatcgt gctcatcgac 240
agcacaccgt accgacagtg gtacgagtcc cactatgcgc tgcccctggg ccgcaagaag 300
ggagccaagc tgactcctga ggaagaagag attttaaaca aaaaacgatc taanaaaaaa 360
aaaacaat
<210> 203
<211> 340
<212> DNA
<213> Homo sapiens
<400> 203
agegtggteg eggeegaggt gaaatggtat teagetteet ggeacttetg gteageaace 60
cagtgttggg caacaaatga tctttgagga acatggtttt aggcggacca caccgcccac 120
aacggccacc cccataaggc ataggccaag accatacccg ccgaatgtag gacaagaagc 180
teteteteag acaaccatet catgggeece attecaggae acttetgagt acateattte 240
atgtcatcct gttggcactg atgaagaacc cttacagttc agggttcctg gaacttctac 300
cagtgccact ctgacaggac ctgcccgggc ggccgctcga
<210> 204
<211> 341
<212> DNA
<213> Homo sapiens
<400> 204
togagoggco gooogggcag gtootgtoag agtggcactg gtagaagtto caggaaccot 60
gaactgtaag ggttcttcat cagtgccaac aggatgacat gaaatgatgt actcagaagt 120
gtcctggaat ggggcccatg agatggttgt ctgagagaga gcttcttgtc ctacattcgg 180
cgggtatggt cttggcctat gccttatggg ggtggccgtt gtgggcggtg tggtccgcct 240
aaaaccatgt teetcaaaga teatttgttg eccaacactg ggttgetgae cagaagtgee 300
aggaagetga ataccattte aceteggeeg egaceaeget a
 <210> 205
 <211> 770
 <212> DNA
 <213> Homo sapiens
```



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<220>
<221> misc feature
<222> 529, 591, 623, 626, 629, 630, 656, 702, 709, 712, 717, 743,
746, 749, 759, 762, 766
<223> n = A, T, C or G
<400> 205
tcgagcggcc gcccgggcag gtctcccttc ttgcggccca ggggcagcgc atagtgggac 60
togtaccact gtoggtacgg tgtgctgtog atgagcacga tgcaattett caccagggtc 120
ttggtacgaa ccagctcgtt attagatgca ttgtagacaa catcgatgat ccttgtttta 180
cgagtacaac actctgagcc ccaggagaaa ttccccacgt ccaacctcag ggcacggtat 240
ttettgttac ctccccgcac acggactgtg tggatgcggc gggggccaag ctgactcctg 300
aggaagaaga gattttaaac aaaaaacgat ctaaaaaaat tcagaagaaa tatgatgaaa 360
ggaaaaagaa tgccaaaatc agcagtctcc tggaggagca gttccagcag ggcaagcttc 420
ttgcgtgcat cgcttcaagg ccgggacagt gtgaccgagc agatggctat gtgctagagg 480
gcaaagaagt ggagttetat ettaagaaaa teagggeeca gaatggtgng tetteaacta 540
atccaaaggg gagtttcaga ccagtgcaat cagcaaaaac attgatactg ntggccaaat 600
ttattggtgc agggcttgca cantangann ggctgggtct tggggcttgg attggnacaa 660
getttggcag cettttettt ggttttgcca aaaacetttt gntgaagang anacetnggg 720
eggaecectt aacegattee aeneenggng gegttetang gneeenettg
<210> 206
<211> 810
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 574, 621, 625, 636, 668, 673, 704, 728, 743, 767, 772, 786,
789, 807, 809, 810
<223> n = A, T, C or G
<400> 206
agegtggteg eggeegaggt etgetgette agegaagggt ttetggeata accaatgata 60
aggetgecaa agaetgttee aataceagea ecagaaceag ceacteetae tgttgeagea 120
cctgcaccaa taaatttggc agcagtatca atgtctctgc tgattgcact ggtctgaaac 180
tecettigga tragetgaga cacaccatte tgggeeetga titteetaag atagaactee 240
aactetttge cetetageae atageeatet geteggteae aetgteeegg eettgaageg 300
atgcacgcaa gaagcttgcc ctgctggaac tgctcctcca ggagactgct gattttggca 360
ttetttttcc tttcatcata tttcttctga atttttttag atcgttttt gtttaaaatc 420
tettetteet caggagtcag ettggeecec geegeateca cacagteegt gtgeggggag 480
gtaacaagaa ataccgtgcc ctgaggttgg acgtggggaa tttctcctgg ggctcagagt 540
ggtgtactcg taaaacaagg atcatcgatg gtgnctacaa tgcatctaat aacgagctgg 600
gtcggaccca aagaacctgg ngaanaaatg gatcgnctca tcgacaggac accgtacccg 660
acagggmac ganteceact atgegettge ecctgggeeg caanaaagga aaactgeeeg 720
ggcggcentc gaaagcccaa ttntggaaaa aatccatcac actgggnggc cngtcgagca 780
                                                                   810
tgcatntana ggggcccatt ccccctnann
<210> 207
 <211> 257
 <212> DNA
 <213> Homo sapiens
 <400> 207
 tegageggee geeegggeag gteeceaace aaggetgeaa eetggatgee atcaaagtet 60
 tetgcaacat ggagactggt gagacetgeg tgtaceceae teageceagt gtggeecaga 120
 agaactggta catcagcaag aaccccaagg acaagaggca tgtctggttc ggcgagagca 180
```



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tgaccgatgg attccagttc gagtatggcg gccagggctc cgaccctgcc gatgtggacc 240
tcggccgcga ccacgct
<210> 208
<211> 257
<212> DNA
<213> Homo sapiens
<400> 208
agegtggteg eggeegaggt ceacategge agggteggag eeetggeege catactegaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
gctgatgtac cagttcttct gggccacact gggctgagtg gggtacacgc aggtctcacc 180
agtetecatg ttgcagaaga etttgatgge atccaggttg cageettggt tggggacetg 240
cccgggcggc cgctcga
<210> 209
<211> 747
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 453, 538, 540, 542, 546, 554, 556, 598, 659, 670, 679, 689,
693, 711, 723, 724, 731, 747
<223> n = A, T, C or G
<400> 209
tegageggee geeegggeag gtecaccaca eccaatteet tgetggtate atggeageeg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtec ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agacceettt egteacceae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatett tgaggaacat ggntttagge ggaccacace gcccacaacg 480
gccaccccca taaggcatag gccaagacca tacccgccga atgtaggaca agaagctntn 540
tntcanacac catntnatgg gccccattcc aggacacttc tgagtacatc atttatgnca 600
tetgtggcac ttgatgaaaa cccttacagt tcagggttct ggaactttta ccaggcctnt 660
tacaggactn ggccggacne cttaagcena ttncaccetg gggcgtteta nggtcccact 720
                                                                    747
cgnncactgg ngaaaatggc tactgtn
<210> 210
<211> 872
<212> DNA
<213> Homo sapiens
 <221> misc feature
 <222> 165, 174, 181, 256, 260, 269, 271, 277, 286, 289, 294, 298,
 300, 301, 303, 308, 311, 321, 325, 328, 329, 333, 338, 342,
 346, 349, 351, 357, 359, 364, 366, 379, 385, 395, 396, 397,
 407, 408, 410, 414, 415, 429, 431, 434, 435, 440, 443
 <223> n = A, T, C or G
 <221> misc feature
 <222> 444, 446, 447, 448, 449, 450, 451, 464, 470, 472, 475, 479,
 483, 484, 485, 488, 494, 496, 497, 504, 508, 509, 511, 513,
 517, 522, 524, 526, 532, 533, 542, 543, 553, 559, 566, 567,
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571, 572, 578, 582, 588, 591, 594, 595, 596, 600, 606
\langle 223 \rangle n = A, T, C or G
<221> misc_feature
<222> 612, 614, 617, 618, 629, 630, 631, 652, 654, 655, 661, 663,
664, 666, 671, 673, 678, 679, 681, 688, 690, 691, 698, 706,
707, 708, 714, 719, 721, 723, 726, 741, 751, 761, 762, 769,
770, 778, 779, 781, 782, 785, 791, 802, 807, 808, 812
<223> n = A, T, C \text{ or } G
<221> misc feature
<222> 815, 820, 827, 828, 838, 841, 844, 851, 857, 864, 866, 869,
<223> n = A, T, C or G
<400> 210
agegtggteg eggeegaggt ceactagagg tetgtgtgee attgeecagg cagagtetet 60
gcgttacaaa ctcctaggag ggcttgctgt gcggagggcc tgctatggtg tgctgcggtt 120
catcatggag agtggggcca aaggctgcga ggttgtggtg tctgngaaac tccnaggaca 180
ngagggetaa attecatgaa gtttgtggat ggeetgatga tecacaateg gagaeeetgt 240
taactactac cgtctnacen cctgctgtnc nccccenttt ctgctnaana catngggntn 300
ntnettgnee nteettgggt ngaanatnna atngeetnee enttentane netaetngnt 360
ccananttgg cctttaaana atccnccttg ccttnnncac tgttcanntn tttnntcgta 420
aaccetatna nttnnattan atnntnnnnn neteaceece etenteattn ancenatang 480
ctnnnaantc cttnanncct cccncccnnt ncnctcntac tnantncttc tnncccatta 540
ennagetett tentttaana taatgnngee nngetetnea thtetaenat ntgnnnaath 600
cccccncccc cnancgnntt tttgacctnn naacctcctt tcctcttccc tncnnaaatt 660
nonnantice nentteenne nttteggnin nteceainet tiecannnet teantetane 720
nenetneaac ttatttteet nteatecett nttetttaca nneceeetnn tetaetenne 780
nnttncatta natttgaaac tnccacnnct anttncctcn ctctacnntt ttattttncg 840
                                                                    872
ntenetetae ntaatanttt aatnanttnt en
<210> 211
<211> 517
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 462, 464, 506
<223> n = A, T, C or G
<400> 211
tcgagcggcc gcccgggcag gtctgccaag gagaccctgt tatgctgtgg ggactggctg 60
gggcatggca ggcggctctg gcttcccacc cttctgttct gagatggggg tggtgggcag 120
tateteatet ttgggtteea caatgeteac gtggteagge aggggettet tagggeeaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacaa gcagtgtcaa cgtagtaagt taacagggtc tccgctgtgg 300
atcatcagge catccacaaa cttcatggat ttagecetet gteeteggag ttteecagae 360
accacaacct cgcagccttt ggccccactc tccatgatga accgcagcac accatagcag 420
geceteegea caagcaagee etectaagaa titgtaacge ananactetg etggeaatgg 480
                                                                    517
cacacaaacc tctagtggac ctcggncgcg accacgc
<210> 212
<211> 695
<212> DNA
<213> Homo sapiens
```

<221> misc feature

<220>

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<222> 432, 476, 522, 547, 621, 624, 647, 679
<223> n = A, T, C or G
<400> 212
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ccagacttga catcatatga atcatactgg ggagaatagt tctgaggacc agtagggcat 120
gattcacaga ttccaggggg gccaggagaa ccaggggacc ctggttgtcc tggaatacca 180
gggtcaccat ttctcccagg aataccagga gggcctggat ctcccttggg gccttgaggt 240
ccttgaccat taggaggcg agtaggagca gttggaggct gtgggcaaac tgcacaacat 300
tctccaaatg gaatttctgg gttggggcag tctaattctt gatccgtcac atattatgtc 360
atcgcagaga acggatectg agtcacagae acatatttgg catggttetg gettecagae 420
atctctatcc gncataggac tgaccaagat gggaacatcc tccttcaaca agcttnctgt 480
tgtgccaaaa ataatagtgg gatgaagcag accgagaagt anccagctcc cctttttgca 540
caaagcntca tcatgtctaa atatcagaca tgagacttct ttgggcaaaa aaggagaaaa 600 '
agaaaaagca gttcaaagta nccnccatca agttggttcc ttgcccnttc agcacccggg 660
ccccgttata aaacacctng ggccggaccc ccctt
<210> 213
<211> 804
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 552, 555, 592, 624, 629, 633, 658, 695, 697, 698, 700, 702,
745, 753, 755, 762, 773, 786, 788, 793, 795
<223> n = A,T,C or G
<400> 213
agcgtggtcg cggccgaggt gttttatgac gggcccggtg ctgaagggca gggaacaact 60
tgatggtgct actttgaact gcttttcttt tctccttttt gcacaaagag tctcatgtct 120
qatatttaqa catqatqaqc tttqtqcaaa aggggagctg gctacttctc gctctgcttc 180
atcccactat tattttggca caacaggaag ctgttgaagg aggatgttcc catcttggtc 240
agtectatge ggatagagat gtetggaage cagaaceatg ceaaatatgt gtetgtgaet 300
caggatecgt tetetgegat gacataatat gtgacgatea agaattagae tgeeccaace 360
cagaaattcc atttggagaa tgttgtgcag tttgcccaca gcctccaact gctcctactc 420
gccctcctaa tggtcaagga cctcaaggcc ccaagggaga tccaggccct cctggtattc 480
ctgggagaaa tggtgaccct ggtattccag gacaaccagg gtcccctggt tctcctggcc 540
cccctggaat cnggngaatc atgccctact ggtcctcaaa ctattctccc anatgattca 600
tatgatgtca agtctgggat agcnagtang ganggactcg caggctattc tggaccanac 660
ctgccggggg ggcgttcgaa agcccgaatc tgcananntn cnttcacact ggcggccgtc 720
gagetgettt aaaagggeea tteeneettt agngnggggg antacaatta etnggeggeg 780
                                                                   804
ttttanancg cgngnctggg aaat
<210> 214
<211> 594
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 452, 509, 585
<223> n = A, T, C or G
<400> 214
agcgtggtcg cggccgaggt.ccacatcggc agggtcggag ccctggccgc catactcgaa 60
```



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ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
gctgatgtac cagttcttct gggccacact gggctgagtg gggtacacgc aggtctcacc 180
agtetecatg ttgcagaaga etttgatgge atccaggttg cageettggt tgggggtcaat 240
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ggggttettg eggetgeeet etgggeteeg gatgtteteg atetgetgge teaggetett 360
gagggtggtg tecacetega ggtcaeggte acgaaceaca ttggcatcat cageeeggta 420
gtageggeca ccategtgag cettetettg angtggetgg ggeaggaact gaagtegaaa 480
ccagegetgg gaggaccagg gggaccaana ggtccaggaa gggcccgggg gggaccaaca 540
ggaccagcat caccaagtgc gacccgcgag aacctgcccg gccgnccgct cgaa
<210> 215
<211> 590
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 8, 9
<223> n = A, T, C or G
<400> 215
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cccggccctc ctggacctcc tggtccccct ggtcctccca gcgctggttt cgacttcagc 120
tteetgeece agecacetea agagaagget cacgatggtg geegetaeta eegggetgat 180
gatgccaatg tggttcgtga ccgtgacctc gaggtggaca ccaccctcaa gagcctgagc 240
cagcagateg agaacateeg gageceagag ggcageegca agaaceeege eegcacetge 300
cytgacctca agatgtgcca ctctgactgg aagagtggag agtactggat tgaccccaac 360
caaggetgea acctggatge catcaaagte ttetgeaaca tggagactgg tgagacetge 420
gtgtacccca ctcagcccag tgtggcccag aagaactggt acatcagcaa gaaccccaag 480
gacaagaggc atgtctggtt cggcgagagc atgaccgatg gattccagtt cgagtatggc 540
                                                                      590
ggccagggct cccaccctgc cgatgtggac ctccggccgc gaccaccctt
<210> 216
<211> 801
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 2, 22, 25, 26, 328, 373, 385, 440, 473, 534, 571, 572, 573,
582, 587, 589, 593, 600, 605, 617, 633, 642, 653, 672, 681, 685, 696, 699, 709, 715, 717, 726, 731, 739, 742, 745, 758, 769, 772, 778, 780, 788, 789, 791, 793, 796
<223> n = A, T, C or G
<400> 216
tngagcggcc gcccgggcag gntgnnaacg ctggtcctgc tggtcctcct ggcaaggctg 60
gtgaagatgg tcaccctgga aaacccggac gacctggtga gagaggagtt gttggaccac 120
agggtgctcg tggtttccct ggaactcctg gacttcctgg cttcaaaggc attaggggac 180
acaatggtct ggatggattg aagggacagc ccggtgctcc tggtgtgaag ggtgaacctg 240
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gaggaccgtg ttggtgcccc tggcccanac ctcggccgcg accacgctaa gcccgaattt 360
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tggtcatagc tgtttcctgn gtgaaattgt tatccgctca caatttcaca cancatacga 480
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ttaantgaaa tccgccnacc cccggggaaa agncggtttg cngtattggg gcnctttttc 660
cetttecteg gnttacttga nttantgggc tttggncgnt tegggttgng geganenggt 720
```



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tcaacntcac nccaaaggng gnaanacggt tttcccanaa tccgggggnt ancccaangn 780
aaaacatnng ncnaangggc t
<210> 217
<211> 349
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 10, 157, 170
<223> n = A, T, C or G
<400> 217
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gcccacgggc tectgtttga cctggagttc cattttcacc aggggcacca ggttcaccct 120
tcacaccagg agcaccgggc tgtcccttca atccatncag accattgtgn cccctaatgc 180
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<210> 218
<211> 372
<212> DNA
<213> Homo sapiens
<400> 218
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gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
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caageetteg ttgacagagt tgcccaeggt aacaacetet tecegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcggc 360
cqcqaccacq ct
<210> 219
<211> 374
<212> DNA
<213> Homo sapiens
<400> 219
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ctgaaagacc agcagaggca taaggttcgg gaagaggttg ttaccgtggg caactctgtc 120 aacgaaggct tgaaccaacc tacggatgac tcgtgctttg acccctacac agtttcccat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttaggct ttggaagtgg tcatttcaag atgtgattca tctagatggt gccatgacaa 300
tggtgtgaac tacaagattg gagagaagtg ggaccgtcag ggagaaaatg gacctgcccg 360
                                                                      374
ggccggccgc tcga
<210> 220
<211> 828
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
 <222> 8, 9, 557, 571, 587, 588, 601, 642, 643, 647, 654, 664, 681,
 688, 698, 719, 720, 725, 734, 738, 743, 744, 757, 765, 773,
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778, 780, 782, 783, 793, 798, 805, 809, 822, 827
<223> n = A, T, C or G
<400> 220
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gcggcagttg tcacagcgcc agccccgctg gcctccaaag catgtgcagg agcaaatggc 120
accgagatat teettetgee actgttetee tacgtggtat gtetteeeat categtaaca 180
cgttgcctca tgagggtcac acttgaattc tccttttccg ttcccaagac atgtgcagct 240
cattiggctg gctctatagt ttggggaaag tttgttgaaa ctgtgccact gacctttact 300
tecteettet etactggage tttegtacet tecaettetg etgttggtaa aatggtggat 360
cttctatcaa tttcattgac agtacccact tctcccaaac atccagggaa atagtgattt 420
cagagcgatt aggagaacca aattatgggg cagaaataag gggcttttcc acaggttttc 480
ctttggagga agatttcagt ggtgacttta aaagaatact caacagtgtc ttcatcccca 540
tagcaaaaga agaaacngta aatgatggaa ngcttctgga gatgccnnca tttaagggac 600
ncccagaact tcaccatcta caggacctac ttcagtttac annaagncac atantctgac 660
tcanaaagga cccaagtagc nccatggnca gcactttnag cctttcccct ggggaaaann 720
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cnnctggggg gcngttcnac atgcntttna agggcccaat tnccccnt
<210> 221
<211> 476
<212> DNA
<213> Homo sapiens
<400> 221
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ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtgt 180
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ggacggtgag gacgctgacc acacggtacg tgctgttgta ctgctcctcc cgcggctttg 360
tettggcatt atgcacctcc acgccgtcca cgtaccagtt gaacttgacc tcagggtctt 420
cgtggctcac gtccaccacc acgcatgtaa cctcagacct cggccgcgac cacgct
<210> 222
<211> 477
<212> DNA
<213> Homo sapiens
<400> 222
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ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120
geogegggag gageagtaca acageaegta eegtgtggte agegteetea eegteetgea 180
ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc 240
ccccatcgag aaaaccatct ccaaagccaa agggcaagcc ccgagaacca caggtgtaca 300
ccctgcccc atcccgggag gagatgacca agaaccaggt cagcctgacc tgcctggtca 360
aaggetteta teecagegae ategeegtgg agtgggagag caatgggeag eeggagaaca 420
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<210> 223
<211> 361
<212> DNA
<213> Homo sapiens
<400> 223
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ggtacagagc tccgatgggt gaaaccattg acatagagac tgtccctgtc cagggtgtag 120
gggcccagct cagtgatgcc gtgggtcagc tggctcagct tccagtacag ccgctctctg 180
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tccagtccag ggcttttggg gtcaggacga tgggtgcaga cagcatccac tctggtggct 240
gececatect teteaggeet gageaaggte agtetgeaac cagagtacag agagetgaca 300
ctggtgttct tgaacaaggg cataagcaga ccctgaagga cacctcggcc gcgaccacgc 360
<210> 224
<211> 361
<212> DNA
<213> Homo sapiens
<400> 224
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gtgtcagctc tctgtactct ggttgcagac tgaccttgct caggcctgag aaggatgggg 120
cagccaccag agtggatgct gtctgcaccc atcgtcctga ccccaaaagc cctggactgg 180
acagagageg getgtactgg aagetgagee agetgaeeea eggeateaet gagetgggee 240
cctacaccet ggacagggac agtetetatg tcaatggttt cacccategg agetetgtac 300
ccaccaccag caccggggtg gtcagcgagg agccattcaa cctgcccggg cggccgctcg 360
<210> 225
<211> 766
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 574, 610, 631, 643, 657, 660, 666, 688, 712, 735, 747
<223> n = A, T, C or G
<400> 225
agegtggteg eggeegaggt cetgteagag tggeactggt agaagtteea ggaaceetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca gaagtgccag 300
gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgtctgtc tttttccttc caatcagggg ctcgctcttc tgattattct 480
tcagggcaat gacataaatt gtatattcgg tcccggttcc aggccagtaa tagtagcctc 540
tgtgacacca gggcggggcc gagggaccct tctnttggaa gagaccagct tctcatactt 600
 gatgatgagn ccggtaatcc tggcacgtgg nggttgcatg atnccaccaa ggaaatnggn 660
gggggnggac etgeeeggeg geegttenaa ageccaatte cacacattg gnggeegtac 720
 tatggatccc actcngtcca acttggngga atatggcata actttt
 <210> 226
 <211> 364
 <212> DNA
 <213> Homo sapiens
 <400> 226
 tegageggee geeegggeag gteettgace ttttcageaa gtgggaaggt gtaateegte 60
 tecacagaca aggecaggae tegtttgtae cegttgatga tagaatgggg tactgatgea 120
 acagttgggt agccaatctg cagacagaca ctggcaacat tgcggacacc ctccaggaag 180
 cgagaatgca gagtttcctc tgtgatatca agcacttcag ggttgtagat gctgccattg 240
 tegaacacet getggatgae cageecaaag gagaaggggg agatgttgag catgtteage 300
 agegtggctt egetggetce caetttgtct ceagtcttga teagaceteg geegegacea 360
                                                                    364
 cact
```

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<210> 227
<211> 275
<212> DNA
<213> Homo sapiens
<400> 227
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gcccagcaac accaaggtgg acaagagagt tgagcccaaa tcttgtgaca aaactcacac 180
atgeceaccg tgeceageac etgaacteet ggggggaccg teagtettee tetteecceg 240
cateceett ccaaacetge cegggeggee geteg
<210> 228
<211> 275
<212> DNA
<213> Homo sapiens
<400> 228
cgagcggccg cccgggcagg tttggaaggg ggatgcgggg gaagaggaag actgacggtc 60
ccccaggag ttcaggtgct gggcacggtg ggcatgtgtg agttttgtca caagatttgg 120
gctcaactct cttgtccacc ttggtgttgc tgggcttgtg atctacgttg caggtgtagg 180
tetgggtgcc gaagttgctg gagggcacgg tcaccacgct gctgagggag tagagtcctg 240
aggactgtag gacagacctc ggccgcgacc acgct
<210> 229
<211> 40
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 1, 4, 5, 13, 15, 17, 29
<223> n = A, T, C or G
                                                                40
nggnnggtcc ggncngncag gaccactcnt cttcgaaata
<210> 230
<211> 208
<212> DNA
<213> Homo sapiens
<400> 230
agegtggteg eggeegaggt ceteacttge etcetgeaaa geacegatag etgegetetg 60
tttgcgaatc agaagttcag tggacttctg ataacgtcta atttcacgga gcgccacagt 180
accaggacct gcccgggcgg ccgctcga
<210> 231
<211> 208
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 33
<223> n = A, T, C or G
```



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<400> 231
tegageggee geeegggeag gteetggtae tgnggegete egtgaaatta gaegttatea 60
gaagtccact gaacttctga ttcgcaaact tcccttccag cgtctggtgc gagaaattgc 120
tcaggacttt aaaacagatc tgcgcttcca gagcgcagct atcggtgctt tgcaggaggc 180
aagtgaggac ctcggccgcg accacgct
<210> 232
<211> 332
<212> DNA
<213> Homo sapiens
<400> 232
tegageggee geeegggeag gtecacateg geagggtegg ageeetggee geeatacteg 60
aactggaatc catcggtcat gctctcgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgt accaqttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atceaqtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
geggggttet tgaeetegge egegaeeaeg et
<210> 233
<211> 415
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 6, 15, 19, 21
<223> n = A, T, C or G
<400> 233
gtgggnttga accentttna netecgettg gtaecgaget eggateeaet agtaacggee 60
gccagtgtgc tggaattcgg cttagcgtgg tcgcggccga ggtcaagaac cccgcccgca 120
cctgccgtga cctcaagatg tgccactctg actggaagag tggagagtac tggattgacc 180
ccaaccaagg ctgcaacctg gatgccatca aagtcttctg caacatggag actggtgaga 240
cctgcgtgta ccccactcag cccagtgtgg cccagaagaa ctggtacatc agcaagaacc 300
ccaaggacaa gaggcatgtc tggttcggcg agagcatgac cgatggattc cagttcgagt 360
atggcggcca gggctccgac cctgccgatg tggacctgcc cgggcggccg ctcga
<210> 234
<211> 776
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 505, 550, 574, 601, 604, 608, 612, 649, 656, 657, 680, 711,
750, 776
<223> n = A, T, C or G
<400> 234
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acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aaqtqqctqc cttcaaqttc ccctqttact qqttacaqaq taaccaccac tcccaaaaat 360
ggaccaggac caacaaaac taaaactgca ggtccagatc aaacagaaat gactattgaa 420
ggcttgcagc ccacagtgga gtatgtggtt aagtgtctat gctcagaatc caagcggaga 480
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72

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gaagtcagcc tctggttcag actgnaagta accaacattg atcgcctaaa ggactggcat 540
tcactgatgn ggatgccgat tccatcaaaa ttgnttggga aaacccacag gggcaagttt 600
ncangtonag gnggacetac tegagecetg aggatggaat cettgactnt teettnneet 660
gatggggaaa aaaaaccttn aaaacttgaa ggacctgccc gggcggccgt ncaaaaccca 720
attccaccc cttgggggcg ttctatgggn cccactcgga ccaaacttgg ggtaan
<210> 235
<211> 805
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 637, 684, 705, 724, 733, 756, 778, 793, 796, 804
<223> n = A, T, C or G
<400> 235
tegageggee geeegggeag gteettgeag etetgeagtg tettetteae cateaggtge 60
agggaatage teatggatte catecteagg getegagtag gteaccetgt acctggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg gcatccacat cagtgaatgc 180
cagteettta gggegateaa tgttggttae tgeagtetga accagagget gaetetetee 240
gettggatte tgagcataga cactaaceae atactecaet gtgggetgea ageetteaat 300
agtcatttct gtttgatctg gacctgcagt tttagttttt gttggtcctg gtccattttt 360
gggagtggtg gttactctgt aaccagtaac aggggaactt gaaggcagcc acttgacact 420
aatgctgttg tcctgaacat cggtcacttg catctgggat ggtttgtcaa tttctgttcg 480
gtaattaatg gaaattggct tgctgcttgc ggggcttgtc tccacggcca gtgacagcat 540
acacagtgat ggtataatca actccaggtt taagccgctg atggtagctg aaactttgct 600
ccaggcacaa gtgaactcct gacagggcta tttcctnctg ttctccgtaa gtgatcctgt 660
aatateteae tgggacagea ggangeatte caaaaetteg ggegngaeee eetaageega 720
attntgcaat atncatcaca ctggcgggcg ctcgancatt cattaaaagg cccaatcncc 780
cctataggga gtntantaca attng
<210> 236
<211> 262
<212> DNA
<213> Homo sapiens
<400> 236
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attgtctccc atttttttgg cttttgaggg ggttcagttt gggttgcttg tctgtttccg 180
ggttgggggg aaagttggtt gggtgggagg gagccaggtt gggatggagg gagtttacag 240
qaaqcaqaca gggccaacgt cg
<210> 237
<211> 372
<212> DNA
<213> Homo sapiens
<400> 237
agegtggteg eggeegaggt ceteaceaga ggtgeeacet acaacateat agtggaggea 60
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aacgaagget tgaaccaace tacggatgac tegtgetttg acceetacae agttteecat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttaggct ttggaagtgg tcatttcaga tgtgattcat ctagatggtg ccatgacaat 300
ggtgtgaact acaagattgg agagaagtgg gaccgtcagg gagaaaatgg acctgcccgg 360
geggeegete ga
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<210> 238
<211> 372
<212> DNA
<213> Homo.sapiens
<400> 238
tegageggce gecegggeag gtecatttte teeetgaegg teceaettet etecaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaageetaag cactggcaca acagtttaaa geetgattea gacattegtt eecacteate 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caagcetteg ttgacagagt tgcccacggt aacaacctct tecegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcggc 360
cgcgaccacg ct
<210> 239
<211> 720
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 478, 557, 563, 566, 620, 660, 663, 672, 673, 684, 693, 695
<223> n = A, T, C or G
<400> 239
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ggagcaaggt tgatttettt cattggteeg gtetteteet tgggggteac cegeaetega 120
tatccagtga gctgaacatt gggtggtgtc cactgggcgc tcaggcttgt gggtgtgacc 180
tgagtgaact tcaggtcagt tggtgcagga atagtggtta ctgcagtctg aaccagaggc 240
tgactctctc cgcttggatt ctgagcatag acactaacca catactccac tgtgggctgc 300
aageetteaa tagteattte tgtttgatet ggacetgeag ttttagtttt tgttggteet 360
ggtccatttt tgggagtggt ggttactctg taaccagtaa caggggaact tgaaggcagc 420
cacttgacac taatgctgtt gtcctgaaca tcggtcactt gcatctggga tggtttgnca 480
atttctgttc ggtaattaat ggaaattggc ttgctgcttg cggggctgtc tccacggcca 540
gtgacagcat acacagngat ggnatnatca actccaagtt taaggccctg atggtaactt 600
 taaacttgct cccagccagn gaacttccgg acagggtatt tcttctggtt ttccgaaagn 660
 gancetggaa tnnteteett ggancagaag ganenteeaa aaettgggee ggaaceeett 720
 <210> 240
 <211> 691
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> 564, 582, 640, 651, 666, 669, 690
 <223> n = A, T, C or G
 <400> 240
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 actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
 cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
 ggtatggtct tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
 aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca gaagtgccag 300
 gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
 ctgtggaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
 gttggggaag ctcgtctgtc tttttccttc caatcagggg ctcgctcttc tgattattct 480
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tcagggcaat gacataaatt gtatattcgg ttcccggttc caggccagta atagtagcct 540
cttgtgacac caggcggggc ccanggacca cttctctggg angagaccca gcttctcata 600
cttgatgatg taacccggta atcctgcacg tggcggctgn catgatacca ncaaggaatt 660
gggtgnggng gacctgcccg gcggccctcn a
<210> 241
<211> 808
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 680, 715, 721, 728, 735, 749, 757, 762, 772, 776, 779, 781,
792, 796, 800, 808
<223> n = A, T, C or G
<400> 241
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagag taaccaccac tcccaaaaat 360
ggaccaggac caacaaaaac taaaactgca ggtccagatc aaacagaaat gactattgaa 420
ggcttgcagc ccacagtgga gtatgtggtt agtgtctatg ctcagaatcc aagcggagag 480
agteagecte tggttcagac tgcagtaacc actatteetg caccaactga cetgaagtte 540
acteaggtea cacceacaag cetgageege cagtggacae cacceaatgt teacteactg 600
gatatcgagt gcgggtgacc cccaaggaga agacccggac ccatgaaaga aatcaacctt 660
gctcctgaca gctcatccgn gggtgtatca ggacttatgg gggactgccc cggcnggccg 720
ntegaaaneg aattnigaaa titeettene aetgggngge gnitegaget inetintana 780
                                                                   808
nggcccaatt cncctntagn gggtcgtn
<210> 242
<211> 26
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 22
<223> n = A, T, C or G
<400> 242
                                                                   26
agcgtggtcg cggccgaggt cnagga
<210> 243
<211> 697
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 496, 541, 624, 662, 679, 688
<223> n = A, T, C or G
<400> 243
tcgagcggcc gcccgggcag gtccaccaca cccaattcct tgctggtatc atggcagccg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
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gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagcccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agaceeettt egteaceeae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatett tgaggaacat ggttttaggc ggaccacacc gcccacaacg 480
ggcaccccca taaggnatag gccaagacca taccccgccg aatgtaggac aagaagctct 540
ntctcaacaa ccatctcatg ggccccattc caggacactt ctgagtacat catttcatgt 600
catcctggtg ggcacttgat gaanaaccct tacagttcag ggttcctgga acttctacca 660
gngccacttc tgacagganc ttgggcgnga ccaccct
<210> 244
<211> 373
<212> DNA
<213> Homo sapiens
<400> 244
agegtggteg eggeegaggt ceattttete cetgaeggte ceaettetet ecaatettgt 60
agttcacacc attgtcatgg caccatctag atgaatcaca tctgaaatga ccacttccaa 120
agcetaagca ctggcacaac agtttaaagc ctgattcaga cattcgttcc cactcatctc 180
caacggcata atgggaaact gtgtaggggt caaagcacga gtcatccgta ggttggttca 240
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ggtctttcag tgcctccact atgatgttgt aggtggcacc tctggtgagg acctgcccgg 360
geggeeeget ega
<210> 245
<211> 307
<212> DNA
<213> Homo sapiens
<400> 245
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ctgcttcctg taaactccct ccatcccaac ctggctccct cccacccaac caactttccc 120
cccaacccgg aaacagacaa gcaacccaaa ctgaaccccc tcaaaagcca aaaaaatqqq 180
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agtttttatc tttgaccaac cgaacatgac caaaaaccaa aagtgacctg cccgggcggc 300
                                                                   307
cgctcga
<210> 246
<211> 372
<212> DNA
<213> Homo sapiens
<400> 246
tegageggee geeegggeag gteeteacea gaggtgeeae etacaacate atagtggagg 60
cactgaaaga ccagcagagg cataaggttc gggaagaggt tgttaccgtg ggcaactctg 120
tcaacgaagg cttgaaccaa cctacggatg actcgtgctt tgacccctac acagtttccc 180
attatgccgt tggagatgag tgggaacgaa tgtctgaatc aggctttaaa ctgttgtgcc 240
agtgcttagg ctttggaagt ggtcatttca gatgtgattc atctagatgg tgccatgaca 300
atggtgtgaa ctacaagatt ggagagaagt gggaccgtca gggagaaaat ggacctcggc 360
cgcgaccacg ct
<210> 247
<211>.348
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> 284, 297, 299, 322, 325, 338, 342, 345
\langle 223 \rangle n = A, T, C or G
<400> 247
tcgagcggcc gcccgggcag gtaccggggt ggtcagcgag gagccattca cactgaactt 60
caccatcaac aacctgcggt atgaggagaa catgcagcac cctggctcca ggaagttcaa 120
caccacggag agggtccttc agggcctgct caggtccctg ttcaagagca ccagtgttgg 180
ccctctgtac tctggctgca gactgacttt gctcagacct gagaaacatg gggcagccac 240
tggagtggac gccatctgca ccctccgcct tgatcccact ggtnctggac tggacanana 300
geggetatac ttgggagetg anecnaacet ttggeggnga encenett
<210> 248
<211> 304
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 125
<223> n = A, T, C or G
<400> 248
gaggactggc tcagctccca gtatagccgc tctctgtcca gtccaggacc agtgggatca 60
aggeggaggg tgcagatggc gtccactcca gtggctgccc catgtttctc aagtetgage 120
aaagncagtc tgcagccaga gtacagaggg ccaacactgg tgctcttgaa cagggacctg 180
agcaggccct gaaggaccct ctccgtggtg ttgaacttcc tggagccagg gtgctgcatg 240
ttctcctcat accgcaggtt gttgatggtg aagttcagtg tgaatggctc ctcgctgacc 300
accc
<210> 249
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 308, 310, 312, 320, 331, 336, 383, 392, 396
<223> n = A, T, C or G
<400> 249
agegtggteg eggeegaggt ccaccacac caatteettg etggtateat ggeageegee 60
acgtgccagg attaccggct acatcatcaa gtatgagaag cctgggtctc ctcccagaga 120
agtggtccct cggccccgcc ctggtgtcac agaggctact attactggcc tggaaccggg 180
aaccgaatat acaatttatg tcattgccct gaagaataat cagaagagcg agcccctgat 240
tggaaggaaa aagacagacg agcttcccca actggtaacc cttccacacc ccaatcttca 300
tggaccanan ancttggatn gtcctttcac nggttnaaaa aacccttttc gccccccac 360
cttggggatt aaccttggga aanggggatt tnaccnttcc
<210> 250
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 338, 357, 361, 369, 388, 394
<223> n = A, T, C \text{ or } G
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<400> 250
tcgagcggcc gcccgggcag gtcctgtcag agtggcactg gtagaagttc caggaaccct 60
gaactgtaag ggttcttcat cagtgccaac aggatgacat gaaatgatgt actcagaagt 120
gtcctggaat ggggcccatg agatggttgt ctgagagaga gcttcttgtc ctacattcgg 180
cgggtatggt cttggcctat gccttatggg ggtggccgtt gtgggcggtg tggtccgcct 240
aaaaccatgt tcctcaaaga tcatttgttg cccaacactg ggttgctgac cagaagtgcc 300
aggaagctga ataccatttc cagtgtcata cccagggngg gtgaccaaag ggggtcnttt 360
ngacctggng aaaggaacca tccaaaanct ctgncccatg
<210> 251
<211> 514
<212> .DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 8, 107, 312, 338, 351, 352, 357, 363, 366, 373, 380, 405,
421, 444, 508
<223> n = A, T, C or G
<400> 251
agcgtggncg cggccgaggt ctgaggatgt aaactcttcc caggggaagg ctgaagtgct 60
gaccatggtg ctactgggtc cttctgagtc agatatgtga ctgatgngaa ctgaagtagg 120
tactgtagat ggtgaagtet.gggtgteeet aaatgetgea teteeagage etteeateat 180
taccgtttct tcttttgcta tgggatgaga cactgttgag tattctctaa agtcaccact 240
gaaatcttcc tccaaaggaa aacctgtgga aaagcccctt atttctgccc cataatttgg 300
ttctcctaat cnctctgaaa tcactatttc cctggaangt ttgggaaaaa nngggcnacc 360
tgncantgga aantggatan aaagatccca ccattttacc caacnagcag aaagtgggaa 420
nggtaccgaa aagctccaag taanaaaaag gagggaagta aaggtcaagt gggcaccagt 480
                                                                    514
ttcaaacaaa actttcccca aactatanaa ccca
<210> 252
<211> 501
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 20, \overline{2}1, 25, 44, 343, 347, 356, 362, 387, 391, 398, 409, 428,
430, 453, 494
<223> n = A, T, C or G
<400> 252
aagcqqccqc ccqgqcagqn ncaqnaqtqc cttcqgqact gggntcaccc ccagqtctqc 60
ggcagttgtc acagcgccag ccccgctggc ctccaaagca tgtgcaggag caaatggcac 120
cqaqatattc cttctqccac tqttctccta cqtqgtatqt cttcccatca tcgtaacacg 180
ttgcctcatg agggtcacac ttgaattctc cttttccgtt cccaagacat gtgcagctca 240
tttggctggc tctatagttt ggggaaagtt tgttgaaact gtgccactga cctttacttc 300
ctccttctct actggagctt tccgtacctt ccacttctgc tgntggnaaa aagggnggaa 360
cntcttatca atttcattgg acagtanece netttetnee caaaacatne aagggaaaat 420
attgattncn agagcggatt aaggaacaac ccnaattatg ggggccagaa ataaaggggg 480
cttttccaca ggtnttttcc t
<210> 253
<211> 226
<212> DNA
<213> Homo sapiens
```



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<400> 253
tcgagcggcc gcccgggcag gtctgcaggc tattgtaagt gttctgagca catatgagat 60
aacctgggcc aagctatgat gttcgatacg ttaggtgtat taaatgcact tttgactgcc 120
atctcagtgg atgacagcct tctcactgac agcagagatc ttcctcactg tgccagtggg 180
caggagaaag agcatgctgc gactggacct cggccgcgac cacgct
<210> 254
<211> 226
<212> DNA
<213> Homo sapiens
<400> 254
agegtggteg eggeegaggt ceagtegeag catgetettt eteetgeeea etggeacagt 60
gaggaagate tetgetgtea gtgagaagge tgteateeac tgagatggea gteaaaagtg 120
catttaatac acctaacgta tcgaacatca tagcttggcc caggttatct catatgtgct 180
cagaacactt acaatagcct gcagacctgc ccgggcggcc gctcga
<210> 255
<211> 427
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 327, 403
<223> n = A, T, C or G
<400> 255
cgagcggccg cccgggcagg tccagactcc aatccagaga accaccaagc cagatgtcag 60
aagctacacc atcacaggtt tacaaccagg cactgactac aagatctacc tgtacacctt 120
gaatgacaat gctcggagct cccctgtggt catcgacgcc tccactgcca ttgatgcacc 180
atccaacctg cgtttcctgg ccaccacacc caattccttg ctggtatcat ggcagccgcc 240
acgtgccagg attaccggct acatcatcaa gtatgagaag cctgggtctc ctcccagaga 300
agtggteeet eggeeeegee etggtgneae agaagetaet attactggee tggaaeeggg 360
aaccgaatat acaatttatg tcattgccct gaagaataat canaagagcg agcccctgat 420
                                                                    427
tggaagg
<210> 256
<211> 535
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 347, 456, 475
\langle 223 \rangle n = A, T, C or G
agcgtggtcg cggccgaggt cctgtcagag tggcactggt agaagttcca ggaaccctga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct gtcttttcc 180
ttccaatcag gggctcgctc ttctgattat tcttcagggc aatgacataa attgtatatt 240
cggttcccgg ttccaggcca gtaatagtag cctctgtgac accagggcgg ggccgaggga 300
ccacttctct gggaggagac ccaggcttct catacttgat gatgtanccg gtaatcctgg 360
caccgtggcg gctgccatga taccagcaag gaattgggtg tggtggccaa gaaacgcagg 420
ttggatggtg catcaatggc agtggaggcg tcgatnacca caggggagct ccgancattg 480
tcattcaagg tggacaggta gaatcttgta atcaggtgcc tggtttgtaa acctg
```

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<210> 257
<211> 544
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 495, 511
<223> n = A, T, C or G
<400> 257
tegageggee geeegggeag gtttegtgae egtgaceteg aggtggaeae eacceteaag 60
agcctgagcc agcagatcga gaacatccgg agcccagagg gcagccgcaa gaaccccgcc 120
cgcacctgcc gtgacctcaa gatgtgccac tctgactgga agagtggaga gtactggatt 180
gaccccaacc aaggetgeaa cetggatgec atcaaagtet tetgcaacat ggagactggt 240
gagacetgeg tgtaceceae teageecagt gtggeecaga agaactggta cateageaag 300
aaccccaagg acaagaagca tgtctggttc ggcgaaagca tgaccgatgg attccagttc 360
gagtatggcg gccagggctc cgacctgcc gatgtggacc tcggccgcga ccacgctaag 420
cccgaattcc agcacactgg cggccgttac tagtgggatc cgagcttcgg taccaagctt 480
ggcgtaatca tgggncatag ctgtttcctg ngtgaaaatg gtattccgct tcacaatttc 540
ccac
<210> 258
<211> 418
<212> DNA .
<213> Homo sapiens
<400> 258
agegtggteg eggeegaggt ceacategge agggteggag ecetggeege catactegaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
gctgatgtac cagttettet gggccacaet gggctgagtg gggtacaege aggteteace 180
agtetecatg ttgcagaaga etttgatgge atecaggttg cageettggt tggggteaat 240
ccaqtactct ccactcttcc agtcagagtg gcacatcttg aggtcacggc aggtgcgggc 300
ggggttettg eggetgeeet etgggeteeg gatgtteteg atetgetgge teaagetett 360
gaagggtggt gtccacctcg aggtcacggt cacgaaacct gcccgggcgg ccgctcga
<210> 259
<211> 377
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature 
<222> 320, 326, 342, 352
<223> n = A, T, C or G
<400> 259
agcgtggtcg cggccgaggt caagaacccc gcccgcacct gccgtgacct caagatgtgc 60
cactctgact ggaagagtgg agagtactgg attgacccca accaaggctg caacctggat 120
gccatcaaag tcttctgcaa catggagact ggtgagacct gcgtgtaccc cactcagccc 180
aqtqtqqccc agaaqaactq qtacatcaqc aagaacccca aggacaagag gcatqtctgg 240
ttcggcgaga gcatgaccga tggattccag ttcgagtatg gcggccaggg ctccgaccct 300
gccgatgtgg acctgcccgn gccggnccgc tcgaaaagcc cnaatttcca gncacacttg 360
gccggccgtt actactg
<210> 260
<211> 332
```

81



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<212> DNA
<213> Homo sapiens
<400> 260
tegageggee geeegggeag gtecacateg geagggtegg agecetggee geeatacteg 60
aactggaatc catcggtcat gctctcgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgt accagttctt ctgggccaca ctgggctgag tgggggtacac gcaggtctca 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
gegggttet tgacctegge egegaceaeg et
<210> 261
<211> 94
<212> DNA
<213> Homo sapiens
<400> 261
cgagcggccg cccgggcagg tccccccct ttttttttt tttttttt ttttttt 60
tttttttt tttttttt ttttttt
<210> 262
<211> 650
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 412, 582, 612, 641, 646
<223> n = A, T, C or G
<400> 262
agcgtggtcg cggccgaggt ctggcattcc ttcgacttct ctccagccga gcttcccaga 60
acatcacata tcactgcaaa aatagcattg catacatgga tcaggccagt ggaaatgtaa 120
agaaggccct gaagctgatg gggtcaaatg aaggtgaatt caaggctgaa ggaaatagca 180
aattcaccta cacagttctg gaggatggtt gcacgaaaca cactggggaa tggagcaaaa 240
cagtetttga atategaaca egeaaggetg tgagactace tattgtagat attgeaceet 300
atgacattgg tggtcctgat caagaatttg gtgtggacgt tggccctgtt tgcttttat 360
aaaccaaact ctatctgaaa tcccaacaaa aaaaatttaa ctccatatgt gntcctcttg 420
ttctaatctt ggcaaccagt gcaagtgacc gacaaaattc cagttattta tttccaaaat 480
gtttggaaac agtataattt gacaaagaaa aaaggatact tctcttttt tggctggtcc 540
accaaataca attcaaaagg ctttttggtt ttattttttt anccaattcc aatttcaaaa 600
tgtctcaatg gngcttataa taaaataaac tttcaccctt nttttntgat
<210> 263
<211> 573
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 453, 458, 544
<223> n = A, T, C or G
<400> 263
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
```



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qaaattqaca aaccatccca qatqcaaqtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagaa gtaaccacca ctcccaaaaa 360
tggaccagga ccaacaaaaa ctaaaactgc aggtccagat caaacagaaa atggactatt 420
gaaggettge ageceacagt ggaagtatgt ggntaggngt etatgeteag aateceaage 480
cggagaaagt cagcettetg gtttagactg cagtaaccaa cattgatcgc cctaaaggac 540
tggncattca cttggatggt ggatgtccaa ttc
<210> 264
<211> 550
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 39, 174, 352, 526
<223> n = A, T, C or G
<400> 264
tcqaqcqqcc qcccqqqcaq qtccttqcaq ctctqcaqnq tcttcttcac catcaggtqc 60
agggaatage teatggatte cateeteagg getegagtag gteaccetgt acetggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagngaatgc 180
cagteettta gggegateaa tgttggttae tgeagtetga accagagget gaetetetee 240
gcttggattc tgagcataga cactaaccac atactccact gtgggctgca agccttcaat 300
agtcatttct gtttgatctg gacctgcagt tttaagtttt tggtggtcct gncccatttt 360
tgggaagtgg ggggttactc tgtaaccagt aacaggggaa cttgaaggca gccacttgac 420
actaatgctg ttgtcctgaa catcggtcac ttgcatctgg ggatggtttt gacaatttct 480
ggttcggcaa attaatggaa attggcttgc tgcttggcgg ggctgnctcc acgggccagt 540
gacagcatac
<210> 265
<211> 596
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 347, 352, 353, 534, 555, 587
<223> n = A, T, C or G
<400> 265
tcgagcggcc gcccgggcag gtccttgcag ctctgcagtg tcttcttcac catcaggtgc 60
agggaatagc tcatggattc catcctcagg gctcgagtag gtcaccctgt acctggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagtgaatgc 180
cagteettta gggegateaa tgttggttac tgeagtetga accagagget gactetetee 240
gettggatte tgagcataga cactaaceae atactecaet gtgggetgea ageetteaat 300
agtcatttct gtttgatctg gacctgcagt tttaagtttt tgttggncct gnnccatttt 360
tggggaaggg gtggttactc ttgtaaccag taacagggga acttgaagca gccacttgac 420
actaatqctq qtqqcctqaa catcqqtcac ttqcatctqq gatggtttgg tcaatttctg 480
tteggtaatt aatgggaaat tggettaetg gettgegggg getgteteca eggneagtga 540
caagcataca caggngatgg gtataatcaa ctccaggttt aaggccnctg atggta
<210> 266
<211> 506
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
```



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<222> 393, 473
<223> n = A, T, C \text{ or } G
<400> 266
agegtggteg eggeegaggt etgggatget eetgetgtea eagtgagata ttacaggate 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gteactggcc gtggagacag ccccgcaagc agtaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagag taaccaccac tcccaaaaat 360
gggaccagga ccaacaaaaa actaaaactg canggtccag atcaaacaga aatgactatt 420
gaaggetige ageceacagt ggagtatgtg ggttagtgte tatgeteaga atnecaageg 480
gagagagtca gcctctggtt cagact
<210> 267
<211> 548
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 346, 358, 432, 510, 512
<223> n = A, T, C or G
<400> 267
tegageggee geeegggeag gteagegete teaggaegte accaecatgg cetgggetet 60
getectecte accetectea etcagggeac agggtectgg geceagtetg ceetgactea 120
gcctccctcc gcgtccgggt ctcctggaca gtcagtcacc atctcctgca ctggaaccag 180
cagtgacgtt ggtgcttatg aatttgtctc ctggtaccaa caacacccag gcaaggcccc 240
caaactcatg atttctgagg tcactaagcg gccctcaggg gtccctgatc gcttctctgg 300
ctccaagtct ggcaacacgg cctccctgac cgtctctggg ctccangctg aggatgangc 360
tgattattac tggaagctca tatgcaggca acaacaattg ggtgttcggc ggaagggacc 420
aagctgaceg tnctaaggtc aagcccaagg cttgcccccc teggtcactc tgttcccacc 480
ctcctctgaa gaagctttca agccaacaan gncacactgg gtgtgtctca taagtggact 540
ttctaccc
<210> 268
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 98, 380, 421, 454, 495, 506, 512, 561, 565, 579
<223> n = A, T, C or G
<400> 268
agcgtggtcg cggccgaggt ctgtagcttc tgtgggactt ccactgctca ggcgtcaggc 60
tcaggtagct gctggccgcg tacttgttgt tgctttgntt ggagggtgtg gtggtctcca 120
ctcccgcctt gacggggctg ctatctgcct tccaggccac tgtcacggct cccgggtaga 180
agteacttat gagacacacc agtgtggcct tgttggcttg aageteetea gaggagggtg 240
ggaacagagt gaccgagggg gcagccttgg gctgacctag gacggtcagc ttggtccctc 300
cgccgaacac ccaattgttg ttgcctgcat atgagctgca gtaataatca gcctcatcct 360
cagectggag cecagagaen gteaagggag geeegtgttt geeaagaett ggaageeaga 420
naagcgatca gggacccctg agggccgctt tacngacctc aaaaaatcat gaatttgggg 480
ggcctttgcc tgggngttgg ttggtnacca gnaaaacaaa atttcataaa gcaccaacgt 540
cactgctggt ttccagtgca ngaanatggt gaactgaant gtcc
```

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<210> 269
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 265, 329
<223> n = A, T, C or G
<400> 269
agegtggteg eggeegaggt eeageateag gageeeegee ttgeeggete tggteatege 60
ctttcttttt gtggcctgaa acgatgtcat caattcgcag tagcagaact gccgtctcca 120
ctgctgtctt ataagtctgc agettcacag ccaatggctc ccatatgccc agttccttca 180
tgtccaccaa agtacccgtc tcaccattta caccccaggt ctcacagttc tcctgggtgt 240
gettggeeeg aagggaggta agtanaegga tggtgetggt cecacagtte tggateaggg 300
tacgaggaat gacctctagg gcctgggcna caagccctgt atggacctgc ccgggcgggc 360
ccgctcga
                                                                   368
<210> 270
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 54, 163, 219, 229, 316
<223> n = A, T, C or G
<400> 270
tegageggee geeegggeag gteeataeag ggetgttgee eaggeeetag aggneattee 60
ttgtaccetg atccagaact gtgggaccag caccatecgt etacttacet ecetteggge 120
caagcacacc caggagaact gtgagacctg gggtgtaaat ggngagacgg gtactttggt 180
ggacatgaag gaactgggca tatgggagcc attggctgng aagctgcana cttataagac 240
agcagtggag acggcagttc tgctactgcg aattgatgac atcgtttcag gccacaaaaa 300
gaaaggegat gaccanagce ggcaaggegg ggctteetga tgetggaeet eggeegeega 360
ccacgctt
                                                                   368
<210> 271
<211> 424
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 279, 329, 362, 384, 400
<223> n = A, T, C or G
<400> 271
agcgtggtcg cggccgaggt ccactagagg tctgtgtgcc attgcccagg cagagtctct 60
gcgttacaaa ctcctaggag ggcttgctgt gcggagggcc tgctatggtg tgctgcggtt 120
catcatggag agtggggcca aaggctgcga ggttgtggtg tctgggaaac tccgaggaca 180
gagggetaaa tecatgaagt ttgtggatgg cetgatgate cacageggag accetgttaa 240
ctactacqtt qacactqctq tqcqccacqt qttqctcana cagqqtqtqc tqggcatcaa 300
ggtgaagatc atgctgccct gggacccanc tggcaaaaat ggcccttaaa aaccccttgc 360
entgaceacg tgaaccattt gtgngaaccc caagatgaan atacttgccc accaccccc 420
attc
```



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<210> 272
<211> 541
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 422, 442, 510, 513, 515, 525
<223> n = A, T, C or G
<400> 272
tegageggee geeegggeag gtetgeeaag gagaceetgt tatgetgtgg ggaetggetg 60
gggcatggca ggcggctctg gcttcccacc cttctgttct gagatggggg tggtgggcag 120
tateteatet ttgggtteca caatgeteac gtggteagge aggggettet tagggeeaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacag cagtgtcaac gtagtagtta acagggtete cgctgtggat 300
catcaggcca tccacaaact tcatggattt agccctctgt cctcggagtt tcccaaaaca 360
ccacaacctc gccagccttt gggccccact tcttcatgaa tgaaaccgca gcacaccatt 420
ancaaggeee tteegeacag gnaageeett eetaaggagt tttgtaaacg caaaaaacte 480
ttgcctgggg caaatgggca cacagacctn tantnggacc ttggnccgcg aaccaccgct 540
t
<210> 273
<211> 579
<212> DNA ·
<213> Homo sapiens
<220>
<221> misc_feature
<222> 223, 265, 277, 308, 329, 346, 360, 366, 429, 448, 517, 524,
531, 578
<223> n = A, T, C or G
<400> 273
agegtggteg eggeegaggt etggeeetee tggeaagget ggtgaagatg gteaccetgg 60
aaaacccgga cgacctggtg agagaggagt tgttggacca cagggtgctc gtggtttccc 120
tggaactcct ggacttcctg gcttcaaagg cattagggga cacaatggtc tggatggatt 180
gaagggacag cccggtgctc ctggtgtgaa gggtgaacct ggngcccctg gtgaaaatgg 240
aactccaggt caaacaggag cccgngggct tcctggngag agaggacgtg ttggtgcccc 300
tggcccanac ctgcccgggc ggccgctcna aaagccgaaa tccagnacac tggcggccgn 360
tactantgga atccgaactt cggtaccaaa gcttggccgt aatcatggcc atagcttgtt 420
ccctggggng gaaattggta ttccgctncc aattccacac aacataccga acccggaaag 480
cattaaagtg taaaagccct gggggggcct aaatgangtg agcntaactc ncatttaatt 540
                                                                   579
ggcgttgcgc ttcactgccc cgcttttcca gtccgggna
<210> 274
<211> 330
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 171
<223> n = A, T, C or G
<400> 274
tegageggee geeegggeag gtetgggeea ggggeaceaa caegteetet eteaceagga 60
ageceaeggg etectgtttg acetggagtt ceatttteae eaggggeaec aggtteaece 120
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ttcacaccag gagcaccggg ctgtcccttc aatccatcca gaccattgtg ncccctaatg 180
cctttgaagc caggaagtcc aggagttcca gggaaaccac gagcaccctg tggtccaaca 240
actcctctct caccaggtcg tccgggtttt ccagggtgac catcttcacc agccttgcca 300
ggagggccag acctcggccg cgaccacgct
<210> 275
<211> 97
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 2, 35, 72
<223> n = A, T, C or G
<400> 275
ancgtggtcg cggccgaggt cctcaccaga ggtgncacct acaacatcat agtggaggca 60
ctgaaagacc ancagaggca taaggttcgg gaagagg
<210> 276
<211> 610
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 358, 360, 363, 382, 424, 433, 464, 468, 477, 491, 499, 511,
558, 584, 588, 590
<223> n = A, T, C or G
tcqaqcqqcc qcccqqqcaq qtccattttc tccctgacgg tcccacttct ctccaatctt 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caagectteg ttgacagagt tgtccaeggt aacaacctct teeegaacct tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcngn 360
congaacaac gottaagece gnattetgea gaataatece ateacacttg geggeegett 420
cgancatgca tentaaaagg ggeeccaatt teeccettat aagngaance gtatttneca 480
atttcactgg ncccgccgnt tttacaaacg ncggtgaact ggggaaaaac cctggcggtt 540
acccaacttt aatcgccntt ggcagcacaa tcccccttt tcgnccancn tgggcgtaaa 600
                                                                   610
taaccgaaaa
<210> 277
<211> 38
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 2, 5, 18, 21, 31
<223> n = A, T, C or G
<400> 277
                                                                   38
anconggtcg cggccgangt nttttttttt
<210> 278
<211> 443
```



```
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 156, 212, 233, 245, 327, 331, 336, 361, 364, 381, 391, 397,
419, 437
<223> n = A,T,C or G
<400> 278
agcgtggtcg cggccgaggt ctgaggttac atgcgtggtg gtggacgtga gccacgaaga 60
ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120
geogegggag gageagtaca acageaegta eegggnggte agegteetea eegteetgea 180
ccagaattgg ttgaatggca aggagtacaa gngcaaggtt tccaacaaag ccntcccagc 240
cccntcgaa aaaaccattt ccaaagccaa agggcagccc cgagaaccac aggtgtacac 300
cctgcccca tcccgggagg aaaagancaa naaccnggtt cagccttaac ttgcttggtc 360
naangetttt tateecaacg nactteecee ntggaantgg gaaaaaccaa tgggeeaane 420
cgaaaaacaa ttacaanaac ccc
<210> 279
<211> 348
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 219, 256, 291, 297, 307, 314, 317
\langle 223 \rangle n = A,T,C or G
<400> 279
tegageggce gecegggeag gtgteggagt ceageaeggg aggegtggte ttgtagttgt 60
teteeggetg eccattgete teccacteca eggegatgte getgggatag aageetttga 120
ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtga 180
acacctgggg ttctcggggc ttgccctttg gttttgaana tggttttctc gatgggggct 240
ggaagggett tgttgnaaac cttgcacttg actcettgcc attcacccag neetggngca 300
ggacggngag gacnetnace acaeggaace gggetggtgg actgetee
<210> 280
<211> 149
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 18, 34, 51, 118, 120, 140
<223> n = A, T, C or G
<400> 280
agegtggtcg cggacgangt cctgtcagag tggnactggt agaagttcca ngaaccctga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagngn 120
cctqqaatqq qgcccatgan atggttgcc
<210> 281
 <211> 404
 <212> DNA
 <213> Homo sapiens
 <220>
```



```
<221> misc_feature
<222> 383, 386, 388, 393
<223> n = A, T, C or G
<400> 281
tegageggec gecegggeag gtecaccaca cecaatteet tgetggtate atggeageeg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtee eteggeeeg ecetggtgte acagaggeta etattactgg eetggaaceg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agacecettt eggeaccee 360
cctgggtatg aacctgggaa aanggnantt aanctttcct ggca
<210> 282
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 320, 341, 424, 450, 459, 487, 498
<223> n = A, T, C or G
<400> 282
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaaggtn ccctggtact gggttacaga ntaaccacca ctcccaaaaa 360
tggaccagga accacaaaaa cttaaactgc agggtccaga tcaaaacaga aatgactatt 420
gaangettge ageceacagt gggagtatgn gggtagtgne tatgetteag aatecaageg 480
qaaaaangtc aagccttntg ggttcaa
<210> 283
<211> 325
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 216, 292, 303, 304
<223> n = A, T, C or G
<400> 283
tegageggee geeegggeag gteettgeag etetgeagtg tettetteae cateaggtge 60
agggaatage teatggatte cateeteagg getegagtag gteaccetgt acctggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagtgaatgc 180
caqteettta gggegateaa tgttggttae tgeagnetga accagagget gactetetee 240
 gcttggattc tgagcataga cactaaccac atactccact gtgggctgca anccttcaat 300
 aanncatttc tgtttgatct ggacc
 <210> 284
 <211> 331
 <212> DNA
 <213> Homo sapiens
 <220>
```

```
<221> misc feature
<222> 54, 59, 63, 121, 312, 327
<223> n = A, T, C or G
<400> 284
tegageggee geeegggeag gtetggtggg gteetggeae aegeaeatgg gggngttgnt 60
ctnatccage tgcccagcce ccattggcga gtttgagaag gtgtgcagca atgacaacaa 120
nacettegae tetteetgee acttetttge cacaaagtge accetggagg geaccaagaa 180
gggccacaag ctccacctgg actacatogg gccttgcaaa tacatccccc cttgcctgga 240
ctctgagctg accgaattcc cccttgcgca tgcgggactg gctcaagaac cgtcctggca 300
cccttgtatg anagggatga agacacnacc c
<210> 285
<211> 509
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 316, 319, 327, 329, 339, 344, 357, 384, 398, 427, 443, 450,
<223> n = A, T, C or G
<400> 285
agegtggteg eggeegaggt etgteetaca gteeteagga etctaeteee teageagegt 60
ggtgaccgtg ccctccagca acttcggcac ccagacctac acctgcaacg tagatcacaa 120
gcccagcaac accaaggtgg acaagagagt tgagcccaaa tcttgtgaca aaactcacac 180
atgeceaceg tgeceageac etgaacteet ggggggaceg teagtettee tetteeceeg 240
cateccett ccaaacetge eegggeggee getegaaage egaatteeag cacaetggeg 300
geeggtacta gtggancena acttggnane caacetggng gaantaatgg geataanetg 360
tttctggggg gaaattggta tccngtttac aattccenca caacatacga gccggaagca 420
taaaagngta aaagcctggg ggnggcctan tgaagtgaag ctaaactcac attaattngc 480
gttgccgctc actggcccgc ttttccagc
<210> 286
<211> 336
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 188, 251, 267
<223> n = A, T, C or G
tcgagcggcc gcccgggcag gtttggaagg gggatgcggg ggaagaggaa gactgacggt 60
cccccagga gttcaggtgc tgggcacggt gggcatgtgt gagttttgtc acaagatttg 120
ggctcaactc tcttgtccac cttggtgttg ctgggcttgt gatctacgtt gcaggtgtag 180
gtctgggngc cgaagttgct ggagggcacg gtcaccacgc tgctgaggga gtagagtcct 240
gaggactgta ngacagacct cggccgngac cacgctaagc cgaattctgc agatatccat 300
 cacactggcg gccgctccga gcatgcattt tagagg
 <210> 287
 <211> 30
 <212> DNA
 <213> Homo sapiens
 <220>
```

```
<221> misc feature
<222> 8, 18
\langle 223 \rangle n = A,T,C or G
<400> 287
                                                                   30
agcgtggncg cggacganga caacaaccc
<210> 288
<211> 316
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 22, 130
<223> n = A, T, C or G
<400> 288
tegageggce geeegggeag gnecacateg geagggtegg agecetggee geeatacteg 60
aactggaatc catcggtcat gctcttgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgn accagttett etgggeeaca etgggetgag tggggtaeac geaggtetea 180
ccagteteca tgttgcagaa gactttgatg gcatccaggt tgcagcettg gttggggtca 240
atcagtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
gcggggttct tgacct
<210> 289
<211> 308
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 36, 165, 191, 195, 218, 235
<223> n = A, T, C or G
<400> 289
agcgtggtcg cggccgaggt ccagcctgga gataanggtg aaggtggtgc ccccggactt 60
ccaggtatag ctggacctcg tggtagccct ggtgagagag gtgaaactgg ccctccagga 120
cctgctggtt tccctggtgc tcctggacag aatggtgaac ctggnggtaa aggagaaaga 180
ggggctccgg ntganaaagg tgaaggaggc cctcctgnat tggcaggggc cccangactt 240
agaggtggag ctggcccccc tggccccgaa ggaggaaagg gtgctgctgg tcctcctggg 300
ccacctgg
<210> 290
<211> 324
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 184
<223> n = A, T, C or G
<400> 290
tegageggce geeegggeag gtetgggeea ggaggaceaa taggaceagt aggaceett 60
qqqccatctt tccctqqqac accatcagca cctggaccgc ctggttcacc cttgtcaccc 120
tttggaccag gacttccaag acetectett tetecaggea tteettgeag aceaggagta 180
ccancagcae caggtggeec aggaggaeca geageaecet tteeteette gggaecaggg 240
```



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ggaccagete cacetetaag teetggggee eetgecaate caggagggee teetteacet 300
ttctcacccg gagcccctct ttct
<210> 291
<211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 249, 267
<223> n = A, T, C or G
<400> 291
tegageggee geeegggeag gtecaeeggg atattegggg gtetggeagg aatgggagge 60
atccagaacg agaaggagac catgcaaagc ctgaacgacc gcctggcctc ttacctggac 120
agagtgagga gcctggagac cgacaaccgg aggctggaga gcaaaatccg ggagcacttg 180
gagaagaagg gaccccaggt cagagactgg agccattact tcaagatcat cgaggacctg 240
agggctcana tcttcgcaaa tactgcngac aatgcccg
<210> 292
<211> 299
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 6, 1\overline{9}, 25, 51, 53, 61, 63, 70, 109, 136, 157, 241, 276
<223> n = A, T, C or G
<400> 292
atgcgnggtc gcggccgang accanctctg gctcatactt gactctaaag ncntcaccag 60
nanttacggn cattgccaat ctgcagaacg atgcgggcat tgtccgcant atttgcgaag 120
atctgagece teaggneete gatgatettg aagtaangge teeagtetet gacetggggt 180
cccttcttct ccaagtgctc ccggattttg ctctccagcc tccggttctc ggtctccaag 240
netteteact etgtecagga aaagaggeea ggeggnegat eagggetttt geatggaet 299
<210> 293
<211> 101
<212> DNA
<213> Homo sapiens
<400> 293
<210> 294
<211> 285
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 64, 103, 110, 237, 282
\langle 223 \rangle n = A, T, C or G
<400> 294
tcgagcggcc gcccgggcag gtctgccaac accaagattg gcccccgccg catccacaca 60
```



```
gttngtgtgc ggggaggtaa caagaaatac cgtgccctga ggntggacgn ggggaatttc 120
teetgggget cagagtgttg tactegtaaa acaaggatea tegatgttgt etacaatgca 180
tctaataacg agctggttcg taccaagacc ctggtgaaga attgcatcgt gctcatngac 240
agcacaccgt accgacagtg ggtaccgaag tcccactatg cncct
<210> 295
<211> 216
<212> DNA
<213> Homo sapiens
<400> 295
tegageggee geeegggeag gtecaceaea eccaatteet tgetggtate atggeageeg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcetgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaag.
<210> 296
<211> 414
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 7, 10, 33, 61, 62, 63, 88, 109, 122, 255, 298, 307, 340,
355, 386, 393
<223> n = A, T, C or G
<400> 296
agcgtgntcn cggccgagga tggggaagct cgnctgtctt tttccttcca atcaggggct 60
nnntcttctg attattcttc agggcaanga cataaattgt atattcggnt cccggttcca 120
gnccagtaat agtagcctct gtgacaccag ggcggggccg agggaccact tctctgggag 180
gagacccagg cttctcatac ttgatgatga agccggtaat cctggcacgt gggcggctgc 240
catgatacca ccaangaatt gggtgtgtgtg gacctgcccg ggcgggccgc tcgaaaancc 300
gaattentge aagaatatee atcacacttg ggegggeegn tegaaccatg catentaaaa 360
 gggccccaat ttccccccta ttaggngaag ccncatttaa caaattccac ttgg
 <210> 297
 <211> 376
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 312, 326, 335, 361
 <223> n = A, T, C or G
 <400> 297
 tegageggee geeegggeag gtetegeggt egeactggtg atgetggtee tgttggteec 60
 cccggccctc ctggacctcc tggtccccct ggtcctccca gcgctggttt cgacttcagc 120
 tteetgeece agecacetea agagaagget caegatggtg geegetacta eegggetgat 180
 gatgecaatg tggttegtga ccgtgacete gaggtggaca ccacceteaa gageettgag 240
 ccagcagaat cgaaaacatt cggaacccaa gaagggcaag cccgcaaaga aaccccgccc 300
 gcacctggcc gngaacctcc aagaangtgc ccacntcttg actgggaaaa aaagggaaaa 360
                                                                    376
 ntacttggaa ttggac
 <210> 298
 <211> 357
 <212> DNA
```



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<213> Homo sapiens
<220>
<221> misc feature
<222> 345, 346
<223> n = A,T,C or G
<400> 298
agegtggteg eggeegaggt ceacategge agggteggag ecetggeege catactegaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
getgatgtac cagttettet gggccacact gggctgagtg gggtacacgc aggtetcacc 180
agtctccatg ttgcagaaga ctttgatggc atccaggttg cagccttggt tggggtcaat 240
ccagtactet ccactettee agteagaagt ggeacatett gaggteaegg cagggtgegg 300
geggggttet tgegggetge eettetggge teeeggaatg ttetnngaac ttgetgg
<210> 299
<211> 307
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 281, 285, 306
<223> n = A, T, C or G
<400> 299
agegtggteg eggeegaggt ceactagagg tetgtgtgee attgeecagg eagagtetet 60
gcgttacaaa ctcctaggag ggcttgctgt gcggagggcc tgctatggtg tgctgcggtt 120
catcatggag agtggggcca aaggctgcga ggttgtggtg tctgggaaac tccgaggaca 180
gagggctaaa tccatgaagt ttgtggatgg cctgatgatc cacagcggag accctgttaa 240
ctactacgtt gacacttgct tgtgcgccac gtgttgctca nacangggtg ggctgggcat 300
caaggng
<210> 300
<211> 351
<212> DNA
<213> Homo sapiens
<400> 300
tcgagcggcc gcccgggcag gtctgccaag gagaccctgt tatgctgtgg ggactggctg 60
gggcatggca ggcggctctg gcttcccacc cttctgttct gagatggggg tggtgggcag 120
tatctcatct ttgggttcca caatgctcac gtggtcaggc aggggcttct tagggccaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacag caagtgtcaa cgtaagtaag ttaacagggt ctccgctgtg 300
gatcatcagg ccatccacaa acttcatgga tttaaccctc tgtcctcgga g
<210> 301
<211> 330
<212> DNA
<213> Homo sapiens
<400> 301
tcgagcggcc gcccgggcag gtgtttcaga ggttccaagg tccactgtgg aggtcccagg 60
agtgctggtg gtgggcacag aggtccgatg ggtgaaacca ttgacataga gactgttcct 120
gtccagggtg taggggccca gctctttgat gccattggcc agttggctca gctcccagta 180
cagccgctct ctgttgagtc cagggctttt ggggtcaaga tgatggatgc agatggcatc 240
cactccagtg getgetecat cettetegga cetgagagag gteagtetge agecagagta 300
                                                                   330
cagagggcca acactggtgt tctttgaata
```

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<210> 302-
<211> 317
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 129, 295
<223> n = A, T, C or G
<400> 302
agegtggteg eggeegaggt etgtaetggg agetaageaa aetgaeeaat gaeattgaag 60
agetgggccc ctacaccetg gacaggaaca gtetetatgt caatggttte acceateaga 120
gctctgtgnc caccaccagc actcctggga cctccacagt ggatttcaga acctcaggga 180
ctccatcctc cctctccagc cccacaatta tggctgctgg ccctctcctg gtaccattca 240
ccctcaactt caccatcacc aacctgcagt atggggagga catgggtcac cctgnctcca 300
ggaagttcaa caccaca
<210> 303
<211> 283
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 139, 146, 195
<223> n = A, T, C or G
<400> 303
tcgagcggcc gcccggacag gtctgggcgg atagcaccgg gcatattttg gaatggatga 60
ggtctggcac cctgagcagt ccagcgagga cttggtctta gttgagcaat ttggctagga 120
ggatagtatg cagcacggnt ctgagnctgt gggatagctg ccatgaagta acctgaagga 180
ggtgctggct ggtangggtt gattacaggg ttgggaacag ctcgtacact tgccattctc 240
                                                                    283
tgcatatact ggttagtgag gtgagcctgg ccctcttctt ttg
<210> 304
<211> 72
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 59
\langle 223 \rangle n = A, T, C or G
agcgtggtcg cggccgaggt gagccacagg tgaccggggc tgaagctggg gctgctggnc 60
ctgctggtcc tg
<210> 305
<211> 245
<212> DNA
<213> Homo sapiens
 <220>
 <221> misc feature
 <222> 5, 11, 22, 98, 102
```



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\langle 223 \rangle n = A, T, C or G
<400> 305
cagengetee naeggggeet gngggaeeaa caacacegtt tteaccetta ggeeetttgg 60
ctcctcttc tcctttagca ccaggttgac cagcagence ancaggacca gcaaatccat 120
tggggccagc aggaccgacc tcaccacgtt caccagggct tccccgagga ccagcaggac 180
cagcaggacc agcagcccca gcttcgcccc ggtcacctgt ggctcacctc ggccgcgacc 240
acgct
<210> 306
<211> 246
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 144, 159
<223> n = A, T, C or G
<400> 306
tcgagcggtc gcccgggcag gtccaccggg atagccgggg gtctggcagg aatgggaggc 60
atccagaacg agaaggagac catgcaaagc ctgaacgacc gcctggcctc ttacctggac 120
agagtgagga gcctggagac cganaaccgg aggctggana gcaaaatccg ggagcacttg 180
gagaagaagg gaccccaggt caagagactg gagccattac ttcaagatca tcgagggacc 240
tggagg
<210> 307
<211> 333
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 5
<223> n = A, T, C or G
<400> 307
agcgnggtcg.cggccgaggt ccagctctgt ctcatacttg actctaaagt catcagcagc 60
aagacgggca ttgtcaatct gcagaacgat gcgggcattg tccgcagtat ttgcgaagat 120
ctgagecete aggtectega tgatettgaa gtaatggete cagtetetga cetggggtee 180
cttettetee aagtgeteee ggattttget etceageete eggttetegg tetecagget 240
cctcactctg tccaggtaag aaggcccagg cggtcgttca ggctttgcat ggtctccttc 300
tcgttctgga tgcctcccat tcctgccaga ccc
<210> 308
<211> 310
<212> DNA
<213> Homo sapiens
<400> 308
tegageggee geeegggeag gteaggaage acattggtet tagageeact geeteetgga 60
ttccacctgt gctgcggaca tctccaggga gtgcagaagg gaagcaggtc aaactgctca 120
gatcagtcag actggctgtt ctcagttctc acctgagcaa ggtcagtctg cagccagagt 180
acagagggcc aacactggtg ttcttgaaca agggcttgag cagaccctgc agaaccctct 240
tccgtggtgt tgaacttcct ggaaaccagg gtgttgcatg tttttcctca taatgcaagg 300
                                                                    310
ttggtgatgg
```



```
<211> 429
<212> DNA
<213> Homo sapiens
<400> 309
agegtggteg eggeegaggt ceacategge agggteggag eeetggeege catactegaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
gctgatgtac cagttettet gggccacact gggctgagtg gggtacaccg caggtetcac 180
cagtetecat gttgcagaag actttgatgg catecaggtt gcagcettgg ttggggtcaa 240
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 Ile Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu
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Leu	Arg 210		Glu	Glu	Asn	Met 215		Pro	Gly	Ser	Arg 220	Lys	Phe	Asn	Thr
Thr 225		Arg	Val	Leu	Gln 230		Leu	Leu	Arg	Pro 235		Phe	Lys	Asn	Thr 240
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Phe	Tyr 530		Gly	Cys	Gln	Leu 535		Ser	Leu	Arg	Pro 540		Lys	Asp	Gly
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	690					695					700			Thr	
705					710					715				Tyr	120
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-	770					775					780			Ser	
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				805					810					Tyr 815	
			820					825					830	Phe	
		835					840					845		Arg	
	850					855					860			Ile	
865					870					875				Суз	880
				885					890					Asn 895	
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ANN 313

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<222> 302, 311
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ccaagaggta atgcactcct tttcccatct ctccaccatc tgtatcctgg ccmagaaaaa 180
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	aaccaaccaa aaagcctccc					
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	ctctactgcc atgactgtca					476
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	aaaaggttgt					
	aggcccaggc tcccagaacc				Lyalyalete	277
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\213\ 110110	saptens					
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ccgggcggcc	gctcga			-		136
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agtetggeta geag	tctgattgaa	gctcaagtca	aggtattcga	gtgatttaag	acctttaaaa	180 184
<210> 333 <211> 384						
<212> DNA						
<213> Homo	sapiens				•	
<400> 333						

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tcaaaacctc caccaccgtg cgcaccacag agattaactt caaggttggg gaggagtttg 180
aggagcagac tgtggatggg aggccctgta agagcctggt gaaatgggag agtgagaata 240
aaatggtctg tgagcagaag ctcctgaagg gagagggccc caagacctcg tggaccagag 300
aactgaccaa cgatggggaa ctgatcctga ccatgacggc ggatgacgtt gtgtgcacca 360
gggtctacgt ccgagagtga gcgg
<210> 334
<211> 169
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 2, 165
<223> n = A, T, C \text{ or } G
<400> 334
cnacaaacag agcagacacc ctggatccgg tcctgctact ggccaggacg gctggaccgt 60
aaaattgaat ticcacttcc tgaccgccgc cagaagagat tgattitetc cactatcact 120
agcaagatga acctetetga ggaggttgae ttggaagaet atgtngeee
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<211> 185
<212> DNA
<213> Homo sapiens
<400> 335
ccaggtttgc agcccaggct gcacatcagg ggactgcctc gcaatacttc atgctgttgc 60
tgctgactga tggtgctgtg acggatgtgg aagccacacg tgaggctgtg gtgcgtgcct 120
cgaacctgcc catgtcagtg atcattgtgg gtgtgggtgg tgctgacttt gaggccatgg 180
                                                                    185
agcag
<210> 336
<211> 358
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 26
<223> n = A, T, C or G
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agagagacct gagctgatga gggctggcgo gatggtggag ttgatgtggt ccactgcctt 180
caggacacct ttgcctaagt aacgctgttt gtctccatcc ctcagctcca gggcctcata 240
gatgcccgta gaggctccac tgggcactgc agcccggaaa agacctttgg cagtatagag 300
atecacetee actgtggggt teeegeggga gteeaggate teeegggeee agatette
 <210> 337
 <211> 271
 <212> DNA
 <213> Homo sapiens
 <220>
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<221> misc_feature
<222> 17
<223> n = A, T, C or G
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gaaatcctgc ccagcatggg attcagaacc tggtctgcaa ccaaatccac cgtcaaagtt 120
catacaggat aaaacaaatt caattgcctt ttccacatta atagcatcaa gcttccccaa 180
caaagccaaa gttgccaccg cacaaaaaga gaatcttgtg tcaatttctc cctactttat 240
aaaagtagat ttttcacatc ccatgaagca g
<210> 338
<211> 326
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 15, 17, 18
<223> n = A, T, C or G
<400> 338
etgtgeteec gaetngnnea teteaggtae caeegaetge aetgggeggg geeetetggg 60
gggaaagget ceacggggca gggatacate tegaggecag teatectetg gaggeagece 120
aatcaggtca aagattttgc ccaactggtc ggcttcagag tttccacaga agagaggctt 180
tegacgaaac atetetgeaa agatacagee aacaeteeae atgteeacag gtgttgeata 240
tgtggactgc agaagaactt cgggagctcg gtaccagagt gtaacaacca cgggtgtaag 300
tgccatctgg tagctgtaga ttctgg
<210> 339
<211> 260
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 47, 54, 60, 69, 90, 91, 96, 113, 117, 119, 195
<223> n = A, T, C \text{ or } G
<400> 339
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caaggacgnc acatttccac ttgcgaatgn nctcanggct catcttgaag aanaagnanc 120
ccaagtgctg gatcccagac tcgggggtaa ccttgtgggt aagagctcat ccagtttatg 180
ctttaggacg tccanctact cgggggagct ggaagcctgc gtggatgcgg ccctgctgga 240
cctcggccgc gaccacgcta
                                                                   260
<210> 340
<211> 220
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 15, 18
<223> n = A, T, C or G
<400> 340
ctggaagccc ggctnggnct ggcagcggaa ggagccaggc aggttcacgc agcggtgctg 60
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```
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atcagggcag gtgcactgat aggagccagg caagttatgg cagtcctggc tggggcgaca 180
gtcgtgcagg gcctgggcac actcgtccac atccacacag
<210> 341
<211> 384
<212> DNA
<213> Homo sapiens
<400> 341
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gatggagett cacacgattt ceteetgegg cageggegaa ggteetetae tgetacaceg 120
ggegteacca gtggcccgtc tgcctcagga actcctccga gtgagggagg agggggctcc 180
ttteccagga tcaaggccac agggaggaag attgcacggg cactgttetg aggaggaage 240
eccepttggct tacagaagtc atggtgttca taccagatgt gggtagccat cctgaatggt 300
ggcaattata tcacattgag acagaaattc agaaagggag ccagccaccc tggggcagtg 360
aagtgccact ggtttaccag acag
<210> 342
<211> 245
<212> DNA
<213> Homo sapiens
<400> 342
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tgtaaccaac aagaatgacc ccaagtccat caactctcga gtcttcattg gaaacctcaa 120
cacagetetg gtgaagaaat cagatgtgga gaccatette tetaagtatg geegtgtgge 180
cggctgttct gtgcacaagg gctatgcctt tgttcagtac tccaatgagc gccatgcccg 240
ggcag
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<211> 611
<212> DNA
<213> Homo sapiens
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tctcagccat ctttgaagct tgaaagaaga gtctttggta ttttgtaaac gttagcagac 120
tttcctgcca gtgtcagaaa atcctattta tgaatcctgt cggtattcct tggtatctga 180
aaaaaatacc aaatagtacc atacatgagt tatttctaag tttgaaaaat aaaaagaaat 240
tgcatcacac taattacaaa atacaagttc tggaaaaaat atttttcttc attttaaaac 300
tttttttaac taataatggc tttgaaagaa gaggcttaat ttggggggtgg taactaaaat 360
caaaagaaat gattgacttg agggtctctg tttggtaaga atacatcatt agcttaaata 420
agcagcagaa ggttagtttt aattatgtag cttctgttaa tattaagtgt tttttgtctg 480
ttttacctca atttgaacag ataagtttgc ctgcatgctg gacatgcctc agaaccatga 540
atagecegta etagatettg ggaacatgga tettagagte etttggaata agttettata 600
taaatacccc c
<210> 344
<211> 311
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 1, 275, 284, 296, 297, 300
<223> n = A, T, C or G
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aacctgactg caaagtggga agaattacca caactgaaga ctttaaacat ctggctcgca 180
agctgactca cggtgttatg aataaggagc tgaagtactg taagaatcct gaggacctgg 240
agtgcaatga gaatgtgaaa cacaaaacca aggantacat taanaagtac atgcannaan 300
tttggggctt g
<210> 345
<211> 201
<212> DNA
<213> Homo sapiens
<400> 345
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aatgtcacca tgagtgtgga tgctgagtgt gtgcccatgg tcagggacct tctcaggtac 120
ttctactccc gaaggattga catcaccctg tcgtcagtca agtgcttcca caagctggcc 180
tctgcctatg gggccaggca g
<210> 346
<211> 370
<212> DNA
<213> Homo sapiens
<400> 346
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tctcttcaga atgttctgga gcagcagttt gaggcgggtg atgcgttgga agggcagaat 120
cagaaaggac ttgagggaaa ggcgctggca gacggggtcg ctctccagct tctccaagac 180
ctcccggaaa ttgctgttgc tattcatcag gctctggaag gtgcgttcct gataggtctg 240
gttggtgaca taaggcaggt agacccggcg gaagtctggg gcgtggttca ggactacgtc 300
acatacttgg aaggagaaga tattgttctc aaagttctct tccaggtctg aaaggaacgt 360
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<210> 347
<211> 416
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 416
<223> n = A, T, C or G
<400> 347
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ccccatttga acaagcaaag aaggtgataa ccatgtttgt acagcgacag gtgtttgctg 120
agaacaagga tgagattgct ttagtcctgt ttggtacaga tggcactgac aatccccttt 180
ctggtgggga tcagtatcag aacatcacag tgcacagaca tctgatgcta ccagattttg 240
atttgctgga ggacattgaa agcaaaatcc aaccaggttc tcaacaggct gacttcctgg 300
atgcactaat cgtgagcatg gatgtgattc aacatgaaac aataggaaag aagtttggag 360
aagaggcata ttgaaatatt cactgacctc aagcagcccg attcagcaaa agtcan
<210> 348
<211> 351
<212> DNA
<213> Homo sapiens
<400> 348
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cagttggatg ctctcctgga ggctctgaaa ttgaaacggg caggaaatag tctggcagcc 120
tctacagcag aagaaacggc aggcagtgcc cagggacgag caggagacag atgccttcct 180
cttgtctcaa ctgcaaagag gcgttccttc ctctttcact aatcctcctc agcacagacc 240
ctttacgggt gtcaggctgg gggacagtaa ggtctttccc ttcccacaag gccatatctc 300
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<210> 349
<211> 207
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 1
<223> n = A, T, C or G
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tgaccagtga gattgcactg ctgcagtcca ggctgaagac agagggctct gatctgtgcg 120
acagagtgag cgaaatgcag aagctggatg cacaggtcaa ggagctggtg ctgaagtcgg 180
cggtggaggc tgagcgcctg gtggctg
<210> 350
<211> 323
<212> DNA
<213> Homo sapiens
<400> 350
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gagacetggg gtgtaaatgg tgagacgggt actttggtgg acatgaagga actgggcata 180
tgggagccat tggctgtgaa gctgcagact tataagacag cagtggagac ggcagttctg 240
ctactgcgaa ttgatgacat cgtttcaggc cacgaaaaga aaggcgatga ccagagccgg 300
caaggcgggg ctcctgatgc tgg
<210> 351
<211> 353
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 12, 25, 39, 42
<223> n = A, T, C or G
<400> 351
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tgtttttgtt ttgtagggtt tttttccttc tccacctctc cctgtctctt ttgctccatg 120
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teeggacteg cetgettggt ggegattete caceggttaa tatggtgegt ecettttte 240
ttttgttgcg aatctgagcc ttcttcctcc agcttctgcc ttttgaactt tgttcttcgg 300
ttctgaaacc atacttttac ctgagtttcc gtgaggctga ggctgtgtgc caa
<210> 352
<211> 467
 <212> DNA
<213> Homo sapiens
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<210> 353 <211> 350 <212> DNA <213> Homo	sapiens					
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<210> 354 <211> 351 <212> DNA <213> Homo	sapiens			·		
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<210> 355 <211> 308 <212> DNA <213> Homo	sapiens					
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<210> 356 <211> 207 <212> DNA <213> Homo	sapiens					
	tgctcccaga ctgcaccgcc					

ggtactttga ataagaacag	cgtggagagg ctaccgctct	aactcctgca gaggagg	ataacttcat	ctatggaggc	tgccggggca	180 207
<210> 357 <211> 188 <212> DNA <213> Homo	sapiens					
<220> <221> misc <222> 25, 2 <223> n = R	9					
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<210> 359 <211> 117 <212> DNA <213> Homo	sapiens					
<220> <221> misc <222> 79, <223> n = 2	98, 100					
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<210> 360 <211> 394 <212> DNA <213> Homo	sapiens					
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<210> 361
<211> 394
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 28, 31
<223> n = A, T, C \text{ or } G
<400> 361
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cagcgaggac ttggtcttag ttgagcaatt tggctaggag gatagtatgc agcacggttc 120
tgagtctgtg ggatagctgc catgaagtaa cctgaaggag gtgctggctg gtaggggttg 180
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tgagcctggc gctcttcttt gcgctgagct aaagctacat acaatggctt tgtggacctc 300
ggccgcgacc acgctaagcc gaattccagc acactggcgg ccgttactag tggatccgag 360
ctcggtacca agcttggcgt aatcatggtc atag
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<211> 268
<212> DNA
<213> Homo sapiens
<400> 362
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tgtttaagga tggtctcggt ggttaggccc actagaataa actgagtcca atacctctac 180
acagttatgt ttaactgggc tctctgacac cgggaggaag gtggcggggt ttaggtgttg 240
caaacttcaa tggttatgcg gggatgtt
<210> 363
<211> 323
<212> DNA
<213> Homo sapiens
<400> 363
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gtttgtaccc gttgatgata gaatggggta ctgatgcaac agttgggtag ccaatctgca 120
gacagacact ggcaacattg cggacaccct ccaggaagcg agaatgcaga gtttcctctg 180
tgatatcaag cacttcaggg ttgtagatgc tgccattgtc gaacacctgc tggatgacca 240
gcccaaagga gaaggggag atgttgagca tgttcagcag cgtggcttcg ctggctccca 300
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ctttgtctcc agtcttgatc aga
<210> 364
<211> 393
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 29
<223> n = A, T, C or G
<400> 364
ccaagetete categteece gtgcgcagng getactgggg gaacaagate ggcaageece 60
acactgtccc ttgcaaggtg acaggccgct gcggctctgt gctggtacgc ctcatcactg 120
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gcatcgatga ctgctacacc tcagcccggg gctgcactgc caccctgggc aacttcgcca 240
aggecacett tgatgecatt tetaagacet acagetacet gacececgae etetggaagg 300
agactgtatt caccaagtct ccctatcagg agttcactga ccacctcgtc aagacccaca 360
ccagagtete egtgeagegg acteaggete eag
<210> 365
<211> 371
<212> DNA
<213> Homo sapiens
<400> 365
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aggagtteet etecaegtea aagtaceage gtgggaagga tgeaeggeaa ggeeeagtga 120
ctgcgttggc ggtgcagtat tcttcatagt tgaacatatc gctggagtgg tcttcagaat 180
cetgeettet gggageactt gggacagagg aatcegetge attectgetg gtggaceteg 240
geogegacca egetaageeg aatteeagea caetggegge egttaetagt ggateegage 300
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ctcacaattc c
<210> 366
<211> 393
<212> DNA
<213> Homo sapiens
<400> 366
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cttcttcagg gatggttgga aggaccatca cactatcccc atccttccaa tcaactgggg 120
tggcaaccet tttttctgct gtcagctgga gagagatgac taccctgaga atctcatcaa 180
agttectgee agtggtaget gggtagagga tagacagett cagettetta teaggaceaa 240
aaacaaacac cacacgagct gccacaggca tgcccttttc atccttctct gctggatcca 300
gcatgcccaa caggatggca agctcccgat tcctatcatc gatgatggga aaaggtaact 360
                                                                   393
tttctgtggg ctcttcacaa ttgtaagcat tga
<210> 367
<211> 327
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 34, 54, 55
<223> n = A, T, C or G
<400> 367
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gcagaacgat gcgggcattg tccacagtat ttgcgaagat ctgagccctc aggtcctcga 120
tgatettgaa gtaatggete cagtetetga eetggggtee ettettetee aagtgeteee 180
ggattttgct ctccagcctc cggttctcgg tctccaggct cctcactctg tccaggtaag 240
aggecaggeg gtegtteagg ctttgeatgg teteettete gttetggatg ceteecatte 300
ctgccagacc cccggctatc ccggtgg
<210> 368
<211> 306
<212> DNA
 <213> Homo sapiens
 <220>
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<221> misc_feature
<222> 24
<223> n = A, T, C or G
<400> 368
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aacggaggca ctgtggccga gaagctggac tgggcccgcg agaggcttga gcagcaggta 180
cctgtgaacc aagtgtttgg gcaggatgag atgatcgacg tcatcggggt gaccaagggc 240
aaaggetaca aaggggteac cagtegttgg cacaccaaga agetgeeeeg caagacccac 300
cgagga
<210> 369
<211> 394
<212> DNA
<213> Homo sapiens
<400> 369
tegaceeaca ceggaaeacg gagagetggg ceageattgg caettgatag gattteeegt 60
eggetgeeac gaaagtgegt ttetttgtgt tetegggttg gaacegtgat ttecacagae 120
cettgaaata cactgegttg aegaggacea gtetggtqag cacaccatca ataagatetg 180
gggacagcag attgtcaatc atatccctgg tttcattttt aacccatgca ttgatggaat 240
cacaggeaga ggctggatec teaaagttea catteeggae eteacaetgg aacacatett 300
tgttccttgt aacaaaaggc acttcaattt cagaggcatt cttaacaaac acggcgttag 360
ccactgtcac aatgtcttta ttcttcttgg agac
<210> 370
<211> 653
<212> DNA
<213> Homo sapiens
<400> 370
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ctggtgtcac agaggctact attactggcc tggaaccggg aaccgaatat acaatttatg 180
tcattgccct gaagaataat cagaagagcg agcccctgat tggaaggaaa aagacagacg 240
agettececa aetggtaace ettecacace ecaatettea tggaceagag atettggatg 300
tteetteeae agtteaaaag acceettteg teacceaece tgggtatgae actggaaatg 360
gtattcagct tcctggcact tctggtcagc aacccagtgt tgggcaacaa atgatctttg 420
aggaacatgg ttttaggcgg accacaccgc ccacaacggc caccccata aggcataggc 480
caagaccata cccgccgaat gtaggacaag aagctetete tcagacaacc ateteatggg 540
ccccattcca ggacacttct gagtacatca tttcatgtca tcctgttggc actgatgaag 600
aaccettaca gttcagggtt cctggaactt ctaccagtgc cactctgaca gga
<210> 371
<211> 268
<212> DNA
<213> Homo sapiens
<400> 371
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getecacetg gaetacateg ggeettgeaa atacateece cettgeetgg actetgaget 180
gaccgaattc cccctgcgca tgcgggactg gctcaagaac gtcctggtca ccctgtatga 240
gagggatgag gacaacaacc ttctgact
<210> 372
<211> 392
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<212> DNA
<213> Homo sapiens
<400> 372
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ggaactggtc cccctggtcc cgaaggagga aagggtgctg ctggtcctcc tgggccacct 120
ggtgctgctg gtactcctgg tctgcaagga atgcctggag aaagaggagg tcttggaagt 180
cetggtccaa agggtgacaa gggtgaacca ggcggtccag gtgctgatgg tgtcccaggg 240
aaagatggcc caaggggtcc tactggtcct attggtcctc ctggcccagc tggccagcct 300
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cctggtgaga gaggtgaaac ctcggccgcg ac
<210> 373
<211> 388
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 30
<223> n = A, T, C or G
<400> 373
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ccaggtcagc gatgaaggta tcttcagtct cccccgaacg atgagacacc atgacgcccc 120
aaccattggc ctgggccagc ttgcacgcct gaagagactc ggtcacggag ccaatctggt 180
tgactttgag caggaggcag ttgcaggact tctcgttcac ggccttggcg atcctctttg 240
ggttggtcac tgtgagatca tcccccacta cctggattcc tgcactggct gtgaacttct 300
gccaagetee ceagteatee tggtcaaagg gatettegat agacaceaet gggtagteet 360
tgatgaagga cttgtacagg tcagccag
<210> 374
<211> 393
<212> DNA
<213> Homo sapiens
<400> 374
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gcatcaaggt agacaagggc gtggtccccc tggcagggac aaatggcgag actaccaccc 180
aagggttgga tgggctgtct gagcgctgtg cccagtacaa gaaggacgga gctgacttcg 240
ccaagtggcg ttgtgtgctg aagattgggg aacacacccc ctcagccctc gccatcatgg 300
aaaatgccaa tgttctggcc cgttatgcca gtatctgcca gcagaatggc attgtgccca 360
tcgtggagcc tgagatcctc cctgatgggg acc
<210> 375
<211> 394
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
 <222>30, \overline{3}3
 <223> n = A, T, C or G
 <400> 375
ccacaaatgg cgtggtccat gtcatcaccn ttnttctgca gcctccagcc aacagacctc 60
aggaaagagg ggatgaactt gcagactctg cgcttgagat cttcaaacaa gcatcagcgt 120
```

ggatgaagca ttctctcaga tgtacatggg	ttagcttgaa tttccacaga	gcactacagg gactgtttga atgagatgtg	aggaatgcac atgttttcaa agccttgtgc	cacggcagct aaccaagtat	ttattagaga ctccgccaat cacactttaa ggagggagag	240 300
<210> 376 <211> 392 <212> DNA <213> Homo	sapiens					
<220> <221> misc_ <222> 30 <223> n = A	-					
ctetteetge getecacetg gacegaatte gagggatgag tgagaatgag	cacttcttg gactacatcg ccctgcgca gacaacaacc	ccacaaagtg ggccttgcaa tgcgggactg ttctgactga aggcaggaga	caccetggag atacatecce getcaagaac gaagcagaag ccaccecgtg	ggcaccaaga ccttgcctgg gtcctggtca ctgcgggtga	agaccttcga agggccacaa actctgagct ccctgtatga agaagatcca cccgggactt	120 180 240 300
<210> 377 <211> 292 <212> DNA <213> Homo	sapiens	,			1	
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<210> 378 <211> 395 <212> DNA <213> Homo	sapiens					
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<210> 379 <211> 223 <212> DNA <213> Homo	sapiens					
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tggttccagc ccacctgccc tccccttttt cgggactctg tattccctct tgggctgacc 180
acagettete cettteccaa ecaataaagt aaceaettte age
<210> 380
<211> 317
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 30, 32
<223> n = A, T, C or G
<400> 380
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gggtgcagga gaacaaggta gaccagtgag gcagaatatg tatcggggat atagaccacg 120
attecgeagg ggeeeteete gecaaagaca geetagagag gaeggeaatg aagaagataa 180
agaaaatcaa ggagatgaga cccaaggtca gcagccacct caacgtcggt accgccgcaa 240
cttcaattac cgacgcagac gcccagaaaa ccctaaacca caagatggca aagagacaaa 300
agcagecgat ccaccag
<210> 381
<211> 392
<212> DNA
<213> Homo sapiens
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<221> misc_feature
\langle 222 \rangle 29, \overline{3}0, 31
<223> n = A, T, C or G
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gggccaagtg ggaggccagg tcagtgtgga ggtggattcc gctccgggca ccgatctcgc 120
caagateetg agtgacatge gaageeaata tgaggteatg geegageaga aceggaagga 180
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ctggcggccg ttactagtgg atccgagctc gg
<210> 382
<211> 234
<212> DNA
<213> Homo sapiens
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cegegactte gttcaggtac atgaagaget ccaaggaggt etggtgggtg gtgccateet 180
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<210> 383
<211> 396
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> 66
<223> n = A, T, C or G
<400> 383
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<213> Homo sapiens
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tagcagtgaa ctcaggagcg ggagcagtcc attcaccctg aaattcctcc ttggtcactg 120
cettetcage ageagectge tettettttt caatetette aggatetetg tagaagtaca 180
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<211> 2943
<212> DNA
<213> Homo sapiens
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ccaccactag catteetggg acceccacag tggacetggg aacatetggg actecagttt 240
ctaaacctgg teectegget gecageeete teetggtget atteactete aactteacea 300
tcaccaacct gcggtatgag gagaacatgc agcaccctgg ctccaggaag ttcaacacca 360
cggagagggt ccttcagggc ctggtccctg ttcaagagca ccagtgttgg ccctctgtac 420
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ecaggtetge etateaagea ggtqtteeat gagetgagee ageagaeeea tggeateace 1440
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aatctccagt	atteaccaga	tatgggcaag	gactcaacta	cattcaactc	caccgagggg	TOOL
atectteage	acctdctcad	accettatte	cagaagagca	gcatgggccc	cttctacttg	1/40
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caatateeta	gtgaccaccc	accaacaaa	qaaqqaagga	gaatacaacg	tccagcaaca	2/60
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Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser
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Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu
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Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp
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Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp
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Thr Phe Arg Phe Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu
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Val Thr Val Lys Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val
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Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu
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Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu Met Glu Ser
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Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser Thr Gln His Phe Tyr Leu
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Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro
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Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Leu
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Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys
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Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His Thr Gly Val
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Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu
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Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Phe
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Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp
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Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly
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<213> Homo sapiens

<400> 391

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<212> PRT

<213> Homo sapiens

<400> 392



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<213> Homo sapiens

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 Ala Ser Ser Glu Thr Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln
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 Pro Thr Val Val Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser
                               185
 Glu Val Ser Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met
                           200
                                             205
 Lys Val Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser
             215
                                            220
 Cys Met Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val
                    230
                                        235
 Thr Glu Ser Glu Ile Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser
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 Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu
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                                                   270
 Leu Pro Leu Ser Pro Tyr Leu Met Leu Lys
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 Ile Ile Leu Ala
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 Ser Gly Arg His
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Ile Lys Leu Ser
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Leu Gly Leu Val
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Gln Val Ile Val
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<210> 402

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Lys Gly Lys Gly Asn
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Met Pro Glu Val
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Arg Cys Glu Ala
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Ala Ser Gln Val
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Thr Ser Phe Glu
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Ser Val Leu Tyr
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<213> Homo sapiens
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Ile Glu Asn Asp
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Glu Ser Glu Ile
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Lys Ala Ser Leu
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Leu Met Leu Lys
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Lys Leu Ser
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Val Ile Val
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Met Pro Glu Val Asn Val Asp Tyr Asn Ala Ser Ser Glu Thr Leu Arg
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Cys Glu Ala Pro Arg Trp Phe Pro Gln Pro Thr Val Val Trp Ala Ser
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Gln Val Asp Gln Gly Ala Asn Phe Ser Glu Val Ser Asn Thr Ser Phe
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Glu
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Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile
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Leu Leu Asn Ser Lys Ala Ser Leu Cys Val
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Ser Leu Cys Val Ser Ser Phe Phe Ala Ile
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Val Leu Tyr Asn Val Thr Ile Asn Asn Thr
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<213> Homo sapiens ·

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Leu Leu Pro Leu Ser Pro Tyr Leu Met Leu
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Cys Met Ile Glu Asn Asp Ile Ala Lys Ala
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Lys Thr Gly Ala Phe Ser Met Pro Glu Val
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Trp Ala Leu Leu Pro Leu Ser Pro Tyr Leu
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Ala Leu Leu Pro Leu Ser Pro Tyr Leu Met
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Gln Leu Leu Asn Ser Lys Ala Ser Leu Cys
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Trp Leu Lys Glu Gly Val Leu Gly Leu Val
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Ala Pro	Gly	Ser	Ser	Thr 70	Pro	Arg	Arg	Gly	Ser 75	Phe	Arg	Ala	Trp	Ser 80	
Leu Phe	: Lуз	Ser	Thr 85	Ser	Val	Gly	Pro	Leu 90	Tyr	Ser	Gly	Суз	Arg 95	Leu	
					T	Agn	Glv	Thr	Ala	Thr	Gly	Val	Asp	Ala	
Thr Leu	Leu	Arg 100	Pro	Glu	nys	ıwp	105					110		1110	
Thr Lev		100					105		Pro	Arg	Leu 125	•	Arg		
	Thr 115	100 His	His	Pro	Asp	Pro 120	105 Lys	Ser			125	Asp		Glu	
Ile Cys	Thr 115 Tyr	100 His Trp	His Glu	Pro Leu	Asp Ser 135	Pro 120 Gln	105 Lys Leu	Ser Thr	His	Asn 140	125 Ile	Asp Thr	Glu	Glu Leu	

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				405					410					Pro 415	
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		595	j				600	t				605	•		Glu Asp
-	610)				615	,				620)			Asp
Pro 625		Ser	Ser	GLU	630		rnr	теп	теп	635		, 116	. 111	·	640

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<213> Homo sapiens

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 Gly
 Cys

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 Thr
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 Arg
 Pro
 Glu
 Lys
 Asp
 Gly
 Ala
 Ala
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 Thr
 Thr

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		130	Leu	Arg			135					140				
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				Pro	245					250					233	
				Gly 260					265					210		
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	305			Leu		310					315					320
				Leu	325					330					222	
				Thr 340					345					350		
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			515	,				520)				520)		His Tvr
		530)				535	,				540	,			Tyr Glv
	545	,				550	}				555)				Gly 560
	Va]	. Val	. Ser	GIU	565		rne	; INI	. neu	570)	_ 111		- 1101	575	Leu

Arg	Tyr	Met	Ala 580	Asp	Met	Gly	Gln	Pro 585	Gly	Ser	Leu	Lys	Phe 590	Asn	Ile
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Leu	Ser	Gln	Gln 660	Thr	His	Gly	İle	Thr 665	Arg	Leu	Gly	Pro	Tyr 670	Ser	Leu
Asp	Lys	Asp 675	Ser	Leu	Tyr	Leu	Asn 680	GЉ	Tyr	Asn	Glu	Pro 685	Gly	Leu	Asp
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Ser 705	Glu	Ala	Thr	Thr	Ala 710	Met	Gly	Tyr	His	Leu 715	Lys	.Thr	Leu	Thr	Leu 720
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			740					745					750	Leu	_
		755					760					765		Суѕ	
	770			_		775	_	,	_		780		_	Val	_
785					790					795				Asp	800
				805					810	•				Thr 815	
			820		•		_	825					830	Gly	_
		835					840					845		Phe	
	850					855			_		860			Glu -	
865				_	870			_	_	875				Tyr	880
				885				_	890					Asn 895	
			900					905					910	Ser	
	_	915					920				•	925		Leu	
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945	Thr	GIU	мет	GIU	950	Ser	vaı	Tyr	GIN		Thr	ser	Ser	Ser	
	Gln	His	Phe	ጥህን		Δen	Phe	Th r	Tla	955 Thr	Δen	Len	Pro	Tyr	960 Ser
1111	GIII	WTO	THE	965	FIO	MOII	FIIE	1111	970	1111	noii	пеп	FIO	975	261
			980					985				_	990	Lys	-
		995					1000)		_		100	5	Ile	_
	1010)				101	5				1020)		Pro	
Arg 1025	_	His	Thr	Gly	Val 1030	_	Ser	Leu	Cys	Asn 103		Ser	Pro	Leu	Ala 1040



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		35			Gln		40					45			
	50				Tyr	55					60				
65					Al a 70					75					80
				85	Pro				90					95	
			100		His			105					TIO		
		115			Phe		120					T22			
	130				Gln	135					140				
1/15					Thr 150					155					100
				165	Thr				170					7.12	
			180		Leu			185					190		
		195			Leu		200					205			
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			260		Asn			265					210		
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	290					295					300				Cys
305					310					315)				7 Val 320
				325					330)				333	
			340)				345	,				350	,	Leu
		355	;				360	1				365	•		Ser
	370)				375	,				380)			Trp
385	;				390					395)				400
				405	•				410)				4 L 3	
			420)			. Суа	425	Gly	у Туз	: Туз	: Glr	430	с ніз Э	Leu
Asp	Lei	1 Glu 43!) Let	ı Glr	1									

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Leu Ser Ser Pro Thr Ile Met Ala Ala Gly Pro Leu Leu Val Pro Phe
                       55
Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Gly
                   70
His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly
Leu Leu Gly Pro Ile Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser
                              105
Gly Cys Arg Leu Thr Ser Leu Arg Ser Lys Lys Asp Gly Ala Ala Thr
                                               125
                          120
Gly Val Asp Ala Ile Cys Ile His His Leu Asp Pro Lys Ser Pro Gly
                      135
                                           140
Leu Asn Arg Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly
                                       155
                   150
Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val
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                                  170
Asn Gly Phe Thr His Arg Thr Ser Val Pro Thr Thr Ser Thr Pro Gly
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Thr Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Leu Pro
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Ala Thr Gln Ser Leu Ala Leu Ser
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Glu Asp Met Arg Arg Thr Gly Ser Arg Lys Phe Asn Thr Met Glu Ser
Val Leu Gln Gly Leu Leu Lys Pro Leu Phe Lys Asn Thr Ser Val Gly
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                                       75
Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Lys Lys Asp
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                                   90
Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Leu Asp Pro
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Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr Trp Glu Leu Ser Lys 120 Leu Thr Asn Asp Ile Glu Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn 140 135 Ser Leu Tyr Val Asn Gly Phe Thr His Gln Ser Ser Val Ser Thr Thr 155 150 Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Arg Thr Ser Val Asp Ser 170 Ile Leu Pro Leu Gln Pro His Asn Tyr Gly Cys Trp Pro Ser Pro Gly 185 Thr Ile His Pro Gln Leu His His His Gln Pro Ala Val Trp Gly Gly 200 205 195 His Gly Ser Pro Trp Leu Gln Glu Val Gln His His Arg Glu Gly Pro 215 220 Ala Gly Ser Ala Trp Ser His Ile Gln Glu His Gln Cys Trp Pro Ser 235 230 Val Leu Trp Leu Gln Thr Asp Leu Ser Gln Val Gln Glu Gly Trp Ser 250 245 Ser His Trp Ser Gly Cys His Leu His Pro Ser Ser

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Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro 245 250 Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr 265 Leu Asn Ser His Leu Gln Ser Pro Val Phe Thr Arg Tyr Gly Gln Gly 280 285 Leu Lys Val His Ser Ile His Arg Gly Gly Ser Phe Ser Asn Trp Ser 295

<210> 487 <211> 294 <212> PRT <213> Homo sapiens

<400> 487

Met Thr Asn Gly Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn 10 Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser Ser Gly Leu Thr Thr 25 Ser Thr Pro Trp Thr Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro 40 Ser Pro Val Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe - 55 Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His 65 70 , 75 Arg Pro Gly Ser Arg Lys Phe Asn Ala Thr Glu Arg Val Leu Gln Gly 90 Leu Leu Ser Pro Ile Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser 105 Gly Cys Arg Leu Thr Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr 120 125 Gly Met Asp Ala Val Cys Leu Tyr His Pro Asn Pro Lys Arg Pro Gly 135 Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn 155 Ile Thr Glu Leu Gly Pro Tyr Ser Leu Asp Arg Asp Ser Leu Tyr Val 165 170 Asn Gly Phe Thr His Gln Asn Ser Val Pro Thr Thr Ser Thr Pro Gly 185 Thr Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Phe Pro 200 Gly His Thr Glu Pro Gly Pro Leu Leu Ile Pro Phe Thr Phe Asn Phe 215 220 Thr Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser 235 230 Arg Lys Phe Asn Ala Thr Glu Arg Val Leu Gln Gly Leu Leu Ser Pro 245 250 Ile Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu 265 Thr Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Met Asp Ala 280 Val Cys Leu Tyr Arg Pro 290

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<210> 489 <211> 178 <212> PRT <213> Homo sapiens

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 Phe

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 Gly
 Ser
 Thr
 Tyr
 Gln
 Leu
 Val
 Asp
 Ile
 His
 Val
 Thr
 Glu
 Ser
 Jul
 

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Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly
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ggatgccatc tgcacccacc gtcttgaccc caaaagccct ggagtggaca gggagcagct 360
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<223> n = A, T, C or G
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His Pro Gln Leu Glu Gln Gln Pro Gln Ser His Ser Trp Cys His Ser
Pro Ser Thr Ser Thr His His Gln Pro Ala Val Arg Gly Gly His Ala
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Ala Pro Gly Ser Arg Lys Phe Asn Ala His Arg Glu Arg Thr Ala Gly 35 40

Ser Cys Ser Asn Pro Arg Ser Gly Ile Ala Val Trp Asn Thr Ser Ile 50 55 60

Gln Ala Ala Asp Xaa Pro His Ser Gly Gln Arg Arg Ile Ala Gln Pro 65 70 75 80

Arg Gln Trp Met Pro Ser Ala His Ile Ala Leu Thr Leu Lys Thr Ser 85 90 95

Asp Trp Thr Glu Ser Asp Cys Thr Gly Ser Xaa Ala Ile Xaa Gln Met 100 105 110

Ala Ser Arg Ser Trp Ala Pro Thr Pro Trp Thr Gly Thr Val Ser Met 115 120 125

Ser Met 130

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<223> Xaa = Any amino acid

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Xaa Ile Pro Ser Ser Asn Ser Ser His Ser Pro Ile His Gly Ala Ile
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His Pro Gln Leu Gln Leu Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met
20 25 30

Arg His Leu Val Pro Gly Ser Ser Thr Arg Thr Glu Arg Glu Leu Gln
35 40 45

Gly Arg Ala Gln Thr Leu Asp Gln Glu Xaa Gln Ser Gly Ile Pro Leu 50 55 60

Phe Arg Leu Gln Thr Ser Leu Thr Gln Ala Arg Glu Gly Xaa Leu Ser 65 70 75 80

His Gly Ser Gly Cys His Leu His Thr Ser Pro Xaa Pro Xaa Arg Pro 85 90 95

Arg Thr Gly Gln Arg Ala Thr Val Leu Gly Ala Glu Gln Ser Asp Lys 100 105 110

Trp His Pro Gly Ala Gly Pro Leu His Pro Gly Pro Glu Gln Ser Leu 115 . 120 125

Cys Gln

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Gly Thr Trp Phe Gln Glu Val Gln Arg Ala Gln Arg Glu Asn Cys Arg
Val Val Leu Lys Pro Xaa Ile Arg Asn Ser Ser Leu Glu Tyr Leu Tyr
Ser Gly Cys Arg Leu Ala Ser Leu Arg Pro Glu Lys Asp Ser Ser Ala
Thr Ala Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Glu Asp Leu
Gly Leu Asp Arg Glu Arg Leu Tyr Trp Glu Leu Ser Asn Leu Thr Asn
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Val Asn
    130
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Pro Thr Thr Ala Gly Pro Leu Leu Met Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met Arg Arg Thr Gly Ser Arg
50 60

Lys Phe Asn Thr Met Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Xaa Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Lys Leu Thr Asn Asp Ile Glu Glu Leu Gly
130 135 140

Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

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<222> 103

<223> Xaa = Any amino acid

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Ser Thr Val Asp Leu Arg Thr Ser Val Thr Pro Ser Ser Leu Ser Ser 20 25 30

Pro Thr Ile Met Ala Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn 35 40 45

Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Gly His Pro Gly 50 55 60

Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly 65 70 75 80

Pro Ile Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg 85 90 . 95

Leu Thr Ser Leu Arg Ser Xaa Lys Asp Gly Ala Ala Thr Gly Val Asp 100 105 110

Ala Ile Cys Ile His His Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg 115 120 125

Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu 130 135 140

Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 576

<211> 122

<212> PRT

<213> Homo sapiens

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Ala Ala Gly Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr Ile Thr 5 10 15

Asn Leu Lys Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg Lys Phe 20 25 30

Asn Thr Thr Glu Arg Val Leu Gln Thr Leu Arg Gly Pro Met Phe Lys
35 40 45

Asn Thr Ser Gly Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu 50 55 60

Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr 65 70 75 80

His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu Tyr 85 90 95

Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu Leu Gly Pro Tyr 100 105 110

Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 115 120

<210> 577

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<222> 11,106,151

<223> Xaa = Any amino acid

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Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Phe Ser Leu Pro Ser 20 25 30

Pro Ala Thr Ala Gly Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr 35 40

Ile Thr Asn Leu Lys Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg.
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Thr Leu Leu Gly Pro Met 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Ser Glu Lys Asp Gly Ala Xaa Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Xaa Ser Leu Tyr Val Asn 145 150 155

<210> 578

<211> 155

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<213> Homo sapiens

<400> 578

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Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro 20 25 30

Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile 35 40 45

Thr Asn Leu Gln Týr Glu Glu Asp Met His His Pro Gly Ser Arg Lys
50 55 60

Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Met Phe 65 70 75 80

Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu 85 90 95

Leu Arg Pro Glu Lys Asn Gly Ala Ala Thr Gly Met Asp Ala Ile Cys 100 105 110

Ser His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu 115 120 125

Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Lys Glu Leu Gly Pro 130 135 140 Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn 150 145 <210> 579 <211> 155 <212> PRT <213> Homo sapiens <220> <221> variant <222> 52,138 <223> Xaa = Any amino acid <400> 579 Gly Phe Thr His Trp Ile Pro Val Pro Thr Ser Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro 25 Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile 40 Thr Asn Leu Xaa Tyr Glu Glu Asp Met His Cys Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Ser Leu Leu Gly Pro Met Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys 105 Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu 120 Tyr Trp Glu Leu Ser Gln Leu Thr Asn Xaa Ile Lys Glu Leu Gly Pro 135 Tyr Thr Leu Asp Ser Asn Ser Leu Tyr Val Asn 150 <210> 580 <211> 156 <212> PRT <213> Homo sapiens <220> <221> variant <222> 23 <223> Xaa = Any amino acid <400> 580 Gly Phe Thr His Gln Thr Ser Ala Pro Asn Thr Ser Thr Pro Gly Thr

5 10 15 Ser Thr Val Asp Leu Gly Xaa Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr Ser Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Met Phe Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asn Gly Ala Ala Thr Gly Met Asp Ala Ile ' Cys Ser His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Lys Glu Leu Gly 135 Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn <210> 581 <211> 156 <212> PRT <213> Homo sapiens <400> 581 Gly Phe Thr His Arg Ser Ser Val Ala Pro Thr Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr Thr Ala Val Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Arg His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Leu Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Ile 90 Ser Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr His His Leu Asn Pro Gln Ser Pro Gly Leu Asp Arg Glu Gln

Leu Tyr Trp Gln Leu Ser Gln Met Thr Asn Gly Ile Lys Glu Leu Gly
130 125

Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 582

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 151

<223> Xaa = Any amino acid

<400> 582

Gly Phe Thr His Arg Ser Ser Gly Leu Thr Thr Ser Thr Pro Trp Thr 5 10 15

Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Pro Val Pro Ser 20 25 30

Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg
50 55 60

Lys Phe Asn Ala Thr Glu Arg Val Leu Gln Gly Leu Leu Ser Pro Ile 65 70 75 80

Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Met Asp Ala Val 100 105 110

Cys Leu Tyr His Pro Asn Pro Lys Arg Pro Gly Leu Asp Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Ser Leu Asp Arg Xaa Ser Leu Tyr Val Asn 145 150 155

<210> 583

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 109,114,117,128,139 <223> Xaa = Any amino acid

<400> 583

Gly Phe Thr His Gln Asn Ser Val Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Phe Pro Gly 20 25 30

His Thr Glu Pro Gly Pro Leu Leu Ile Pro Phe Thr Phe Asn Phe Thr 35 40 45

Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Thr Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Gln Glu Ala Ala Thr Gly Xaa Asp Thr Ile 100 105 110

Cys Xaa His Arg Xaa Asp Pro Ile Gly Pro Gly Leu Asp Arg Glu Xaa 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Xaa Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 584

<211> 156

<212> PRT

<213> Homo sapiens

<400> 584

Gly Phe Asn Pro Trp Ser Ser Val Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Ser Thr Val His Leu Ala Thr Ser Gly Thr Pro Ser Ser Leu Pro Gly 20 25 30

His Thr Ala Pro Val Pro Leu Leu Ile Pro Phe Thr Leu Asn Phe Thr 35 · 40 45

Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95



Leu Leu Arg Pro Glu Lys His Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr Leu Arg Leu Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Arg 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Ser Val Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 585

<211> 156

<212> PRT

<213> Homo sapiens

<400> 585

Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr
5 10 15

Ser Ala Val His Leu Glu Thr Ser Gly Thr Pro Ala Ser Leu Pro Gly 20 25 30

His Thr Ala Pro Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met Arg His Pro Gly Ser Arg 50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Arg Gly Ala Ala Thr Gly Val Asp Thr Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Leu Asn Pro Gly Leu Asp Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Lys Leu Thr Cys Gly Ile Ile Glu Leu Gly 130 135 140

Pro Tyr Leu Leu Asp Arg Gly Ser Leu Tyr Val Asn 145 150 155

<210> 586

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 151,156 <223> Xaa = Any amino acid

<400> 586

Gly Phe Thr His Arg Asn Phe Val Pro Ile Thr Ser Thr Pro Gly Thr 5 10 15

Ser Thr Val His Leu Gly Thr Ser Glu Thr Pro Ser Ser Leu Pro Arg 20 25 30

Pro Ile Val Pro Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Ala Met Arg His Pro Gly Ser Arg
50 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Ile Gly Pro Leu Tyr Ser Ser Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Lys Ala Ala Thr Arg Val Asp Ala Ile 100 105 110

Cys Thr His His Pro Asp Pro Gln Ser Pro Gly Leu Asn Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

<210> 587

<211> 156

<212> PRT

<213> Homo sapiens

<400> 587

Gly Phe Thr His Trp Ser Pro Ile Pro Thr Thr Ser Thr Pro Gly Thr 5 10 15

Ser Ile Val Asn Leu Gly Thr Ser Gly Ile Pro Pro Ser Leu Pro Glu 20 25 30

Thr Thr Ala Thr Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asn Met Gly His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Ile Thr Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Val Ala Thr Arg Val Asp Ala Ile 100 105 110

Cys Thr His Arg Pro Asp Pro Lys Ile Pro Gly Leu Asp Arg Gln Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly
130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 588

<211> 156

<212> PRT

<213> Homo sapiens

<400> 588

Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Thr Pro Gly Thr 5 10 15

Phe Thr Val Gln Pro Glu Thr Ser Glu Thr Pro Ser Ser Leu Pro Gly 20 25 30

Pro Thr Ala Thr Gly Pro Val Leu Leu Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Ile Asn Leu Gln Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg 50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Met Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Ser Ser Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Arg Val Asp Ala Val 100 105 110

Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Arg 115 120 125

Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn 145 150 155

<210> 589

<211> 156

<212> PRT

<213> Homo sapiens

<400> 589

Gly Phe Thr His Gln Ser Ser Met Thr Thr Arg Thr Pro Asp Thr

15 10 Ser Thr Met His Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly Pro Thr Thr Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr 40 Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met His His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Lys Lys Asp Gly Ala Ala Thr Lys Val Asp Ala Ile Cys Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln 120 Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 150 <210> 590 <211> 156 <212> PRT <213> Homo sapiens <220> <221> variant <222> 145 <223> Xaa = Any amino acid <400> 590 Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr Pro Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Val Ser Lys Pro Gly Pro Ser Ala Ala Ser Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr 40 Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Ser Leu

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr

Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly 130 135 140

Xaa Tyr Ala Leu Asp Asn Asp Ser Leu Phe Val Asn 145 150 155

<210> 591

<211> 155

<212> PRT

<213> Homo sapiens

<400> 591

Gly Phe Thr His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr
5 10 15

Pro Thr Val Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser Ile Phe Gly 20 25 30

Pro Ser Ala Ala Ser His Leu Leu Ile Leu Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Trp Pro Gly Ser Arg Lys
50 55 60

Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe 65 70 75 80

Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu 85 90 95

Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys
100 105 110

Thr His Arg Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu 115 120 125

Tyr Leu Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro 130 135 140

Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 592

<211> 134

<212> PRT

<213> Homo sapiens

<400> 592

Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val Val

204

15. 10 Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser Val Lys 70 Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu Asp Lys 120 Asp Ser Leu Tyr Leu Asn 130 <210> 593 <211> 150 <212> PRT <213> Homo sapiens <220> <221> variant <222> 7 <223> Xaa = Any amino acid <400> 593 Gly Tyr Asn Glu Pro Gly Xaa Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp

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Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser 115 120 125

Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg 130 135 140

Asp Ser Leu Phe Ile Asn 145 150

<210> 594

<211> 318

<212> PRT

. <213> Homo sapiens

<220>

<221> variant

<222> 136,248,268

<223> Xaa = Any amino acid

<400> 594

Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn 5 10 15

Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser 20 25 30

Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu 35 40 45

Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr
50 60

Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser 65 70 75 80

Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr 85 90 95

Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp 100 105 110

Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser 115 120 125

Ser Ser Thr Gln His Phe Tyr Xaa Asn Phe Thr Ile Thr Asn Leu Pro 130 135 140

Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn 145 150 155

Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser 165 170 175

Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val 180 185 190 Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro 200

Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg 215

Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser

Ser Val Leu Val Asp Gly Tyr Xaa Pro Asn Arg Asn Glu Pro Leu Thr

Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Xaa Ile Gly Leu Ala 265

Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr 280

Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys

Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln 310

<210> 595

<211> 3451

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> 177, 335, 523, 618, 663, 875, 961, 1001, 1441, 1555, 1560, 1563, 1574, 1585, 2065, 2070, 2683, 2990, 3269, 3381, 3401

<223> Xaa = Any Amino Acid

<400> 595

Ile Arg Asn Ser Ser Leu Glu Tyr Leu Tyr Ser Gly Cys Arg Leu Ala 10

Ser Leu Arg Pro Glu Lys Asp Ser Ser Ala Thr Ala Val Asp Ala Ile 25

Cys Thr His Arg Pro Asp Pro Glu Asp Leu Gly Leu Asp Arg Glu Arg 45 40

Leu Tyr Trp Glu Leu Ser Asn Leu Thr Asn Gly Ile Gln Glu Leu Gly 55 60

Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His 75 70

Arg Ser Ser Met Pro Thr Thr Ser Thr Pro Gly Thr Ser Thr Val Asp 90 85

Val Gly Thr Ser Gly Thr Pro Ser Ser Ser Pro Ser Pro Thr Thr Ala 110 100 105

Gly Pro Leu Leu Met Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu 125 120

Gln Tyr Glu Glu Asp Met Arg Arg Thr Gly Ser Arg Lys Phe Asn Thr 140 135

Met Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu Phe Lys Asn Thr 155 Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro

									170					175	
Xaa	Lys	Asp		165 Ala	Ala	Thr	Gly	Val 185	170 Asp	Ala	Ile	Суѕ	Th <i>x</i> 190	His	Arg
Leu	Asp	Pro	180 Lys	Ser	Pro	Gly	Leu 200		Arg	Glu	Gln	Leu 205		Trp	Glu
Leu	Ser 210	Lys	Leu	Thr	Asn	Asp 215		Glu	Glu	Leu	Gly 220	Pro	Tyr	Thr	Leu
225	Arg				230	Val				235				Ser	240
Ser				245					250					Thr 255	
			260					265					270	Gly	
		275					280					285		Gln	
	290					295					300			Thr	
305					310					315				Ser	320
				325					330					Xaa 335	
			340					345					350	Leu	
		355					360					365		Leu	
	370					375					380			Asp	
385					390					395				Phe	400
				405					410			•		His 415	
			420					425					430	Thr	
		435					440					445		Ser	
_	450					455					460			Thr	
465					470					475				Gly	480
Asp	Arg			485					490					Gly 495	
_			500					505					510		
		515					520					525		Gly	
	530					535					540			Pro	
545					550					555		•		Phe	560
				565					570					Ser 575	
_			580	1				585	,				590		
		595	,				600	1				605	i	Leu	
	610					615	,				620	ı		Ala	
Cys	Thr	His	Arg	Leu	Asp	Pro	рÀа	Ser	Pro	GLY	val	. ASP	AIG	Glu	GIII

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625					630		_		_	635	T 1.	T	Clu		
Leu	Tyr	\mathtt{Trp}	Glu		Ser	Gln	Leu	Thr	Asn	Gly	TTE	ьys	GIU	655	GIJ
_	_	m) .	*	645	B	V	e-~	Lon	650	Val	Asn	Glv			His
Pro	Tyr	Thr		Asp	Arg	Ada	Ser	665	TÄT	Val	11011	رحی	670		
П	Tla	Dro	060 Val	Dro	Thr	Ser	Ser	Thr	Pro	Gly	Thr	Ser		Val	Asp
ırp	116	675	Val	110	1114		680					685			
Ten	Glv	Ser	Glv	Thr	Pro	Ser	Ser	Leu	Pro	Ser	Pro	Thr	Thr	Ala	Gly
	690					695					700				
Pro	Leu	Leu	Val	Pro	Phe	Thr	Leu	Asn	Phe	Thr	Ile	Thr	Asn	Leu	Gln
705					710					112					120
Tyr	Glu	Glu	Asp	Met	His	His	Pro	Gly	Ser	Arg	'nАз	Pne	Asn	735	1111
	_		_	725	~ 3	T	T	C1	730	Mot	Phe	Lvs	Asn		Ser
Glu	Arg	Val		GIn	GTA	теп	теп	745	PLU	Met	FIIG	шуз	750		
17 1	C1	T 011	740	Tur	Ser	Glv	Cvs		Leu	Thr	Leu	Leu	Arg	Pro	Glu
		755					760					165			
T.vs	Asn	Glv	Ala	Ala	Thr	Gly	Met	Asp	Ala	Ile	Cys	Ser	His	Arg	Leu
	770					775					780				
Asp	Pro	Lys	Ser	Pro	Gly	Leu	Asn	Arg	Glu	Gln	Leu	Tyr	Trp	Glu	Leu
795					790					195					000
Ser	Gln	Leu	Thr		Gly	Ile	ГÀЗ	Glu	Leu	Gly	Pro	туг	Thx	ьец 815	Asp
				805	7	_	G1	Dh	810		Ψ×T	Tla	Pro		Pro
Arg	His	Ser	Leu	Tyr	Val	Asn	GTA	825	Thr	His	пр	116	830	V 4.2.	
m la se	C		820	Pro	G1 17	ሞh r	Ser	Thr	Val	Asp	Leu	Gly		Gly	Thr
		235					840					845	•		
Pro	Ser	Ser	Leu	Pro	Ser	Pro	Thr	Thr	Ala	Gly	Pro	Leu	Leu	Val	Pro
	850					855					860				
Phe	Thr	Leu	Asn	Phe	Thr	Ile	Thr	Asn	Lev	Xaa	Tyr	Glu	Glu	Asp	Met
0.55					ጸ7ሰ					875)				000
His	Cys	Pro	Gly			Lys	Phe	Asn	Thi	Thr	GIU	Arg	yaı	895	GIII
		_		885		D1	.	70	890		· Wal	G) s	Pro		
Ser	Leu	Leu			Met	Pne	гуу	905		: Ser	, vai	. 013	910		
C			900	, T.A.	Thr	T.e.1	Ten			c Glu	ı Lvs	: Ast			Ala
Ser	GT7	915) Dea	7117	пеп	920)	,			925	5 -		
Thr	GIV	, Val	Ast	Ala	Ile	Cys	Thr	His	Arg	g Let	a Asp	Pro	Lys	Ser	Pro
	930)				935	,				940)			
Gly	Va.	Asp	Arg	, Glu	Gln	Lev	тух	: Tr	Gl1	ı Leı	ı Seı	Gl:	n Leu	Thr	Asn
945	.				950)				95	•				960
Xaa	ı Ile	е Lys								u Ası	Sei	c Ası	n Sei	: ьес 975	Tyr
				965	, 	~7-	. m.	- Ca.	97		- Des	. ጥኮ	r Sei	_	
۷a.	L Ası	n Gly			Hls	GLI	ı Tnı	98!	S ALL	a PI	J MSI	1 111	990)	Pro
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Pro	s Se	r Pro	o Thi	r Se	Ala	a Gl	y Pro	o Le	u Le	u Va	l Pr	o Ph	e Th	r Lei	a Asn
	10	10				10:	15				TO:	20			
Phe	e Th	r Il	e Th	r Ası	ı Leı	ı Glı	a Ty	r Gl	u Gl	u As	р Ме	t Hi	s Hi	s Pro	Gly
101	25				103	30				10	35				1040
Se	r Ar	g Ly	s Ph			c Thi	r Gl	u Ar	g Va	l Le	u Gl	n Gl	y Pe	u Tei	ı Gly
				10	45				. 10	50				TO:	99
Pr	o Me	t Ph			n Th	r Se	r Va	ı Gl	се Аге	и ье	u Ty	T. 26	10	y ⊂y: 70	s Arg
_	201	7	10	טט ייירייי	~ D~	~ (c) ·	n T.v	~ 7~ TO	65 ո. Gl	רב ע	a Al	a Th			t Asp
гe	u Th		и Бе 75	u AI	y PT	O GT.	и Бу 10	80 80	91	. ,	ىسى مىلىدە م	10	85		
Δ7	a Tì	e Cv	s Se	r Hi	s Ar	g Le	u As	p Pr	о Гу	s Se	r Pr			u As	n Arg
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1100	, 61 v	Pro	Tur	Thr	Len	Asp	Ara	Asn				Val	Asn	Gly	Phe
пеп	GTÄ	LIU	- Y -	1125		·mp	9		1130)	- 4			1135	;
Thr	His	Ατα	Ser	Ser	Val	Ala	Pro	Thr			Pro	Gly	Thr	Ser	Thr
1111	1112	, my	1140		• • • •			1145	,			_	1150)	
Wa l	Zen	T.011	Glv	ምክ r	Ser	Glv	Thr			Ser	Leu	Pro	Ser	Pro	Thr
VUI	ıωp	1155				 4	1160)				1165	5		
Thr	Δla	Val	Pro	Len	Leu	Val			Thr	Leu	Asn	Phe	Thr	Ile	Thr
1111	1170					1175					1180				
Δen	Len	Gln	Tur	Glv	Glu	Asp	Met	Ara	His	Pro	Gly	Ser	Arg	Lys	Phe
1185			-,-	3	1190			_		1195	, -				1200
Asn	Thr	Thr	Glu	Ara	Val	Leu	Gln	Gly	Leu	Leu	Gly	Pro	Leu	Phe	Гуз
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1265	5				1270)				1275	5				1280
Thr	Leu	Asp	Arq	Asn	Ser	Leu	Tyr	Val	Asn	Gly	Phe	Thr	His	Arg	Ser
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	Val	Leu	Gln	Gly 136	1350 Leu 5	Leu	Ser	Pro Leu	Ile 1370 Thr	1355 Phe 0	Lys	Asn	Ser Pro	Ser 1375 Glu	Val 5
Gly	Val Pro	Leu Leu	Gln Tyr 138	Gly 136 Ser	1350 Leu 5 Gly	Deu Cys	Ser Arg	Pro Leu 138	11e 1370 Thr	1359 Phe O Ser	Lys Leu	Asn Arg	Ser Pro 139	Ser 1379 Glu O	Val 5 Lys
Gly	Val Pro	Leu Leu Ala	Gln Tyr 1380 Ala	Gly 136 Ser	1350 Leu 5 Gly	Deu Cys	Ser Arg Asp	Pro Leu 138 Ala	11e 1370 Thr	1359 Phe O Ser	Lys Leu	Asn Arg Tyr	Ser Pro 139	Ser 1375 Glu	Val 5 Lys
Gly Asp	Val Pro Gly	Leu Leu Ala 139	Gln Tyr 1380 Ala	Gly 136 Ser O Thr	1350 Leu 5 Gly Gly	D Leu Cys Met	Ser Arg Asp 140	Pro Leu 138! Ala	Ile 1370 Thr 5 Val	1355 Phe O Ser Cys	Lys Leu Leu	Asn Arg Tyr 140	Ser Pro 139 His	Ser 1379 Glu O Pro	Val 5 Lys Asn
Gly Asp	Val Pro Gly	Leu Leu Ala 139	Gln Tyr 1380 Ala	Gly 136 Ser O Thr	1350 Leu 5 Gly Gly	Leu Cys Met Asp	Ser Arg Asp 140 Arg	Pro Leu 138! Ala	Ile 1370 Thr 5 Val	1355 Phe O Ser Cys	Lys Leu Leu Tyr	Asn Arg Tyr 140 Trp	Ser Pro 139 His	Ser 1379 Glu O	Val 5 Lys Asn
Gly Asp Pro	Val Pro Gly Lys	Leu Leu Ala 139 Arg	Tyr 1380 Ala 5 Pro	Gly 1369 Ser O Thr	1350 Leu 5 Gly Gly Leu	Leu Cys Met Asp	Ser Arg Asp 140 Arg	Pro Leu 1389 Ala O Glu	Ile 1370 Thr 5 Val	1359 Phe O Ser Cys Leu	Lys Leu Leu Tyr 142	Asn Arg Tyr 140 Trp	Pro 139 His 5	Ser 1379 Glu O Pro Leu	Val 5 Lys Asn Ser
Gly Asp Pro Gln	Val Pro Gly Lys 141 Leu	Leu Leu Ala 139 Arg	Tyr 1380 Ala 5 Pro	Gly 1369 Ser O Thr	1350 Leu Gly Gly Leu	Leu Cys Met Asp 141	Ser Arg Asp 140 Arg	Pro Leu 1389 Ala O Glu	Ile 1370 Thr 5 Val	1355 Phe O Ser Cys Leu	Lys Leu Leu Tyr 142 Tyr	Asn Arg Tyr 140 Trp	Pro 139 His 5	Ser 1379 Glu O Pro Leu	Val 5 Lys Asn Ser
Gly Asp Pro Gln 142	Val Pro Gly Lys 141 Leu	Leu Ala 139 Arg O	Gln Tyr 1380 Ala 5 Pro	Gly 1369 Ser Thr Gly	1350 Leu Gly Gly Leu Ile 143	Leu Cys Met Asp 141 Thr	Ser Arg Asp 140 Arg 5	Pro Leu 138: Ala Glu Leu	Ile 1370 Thr 5 Val Gln Gly	1358 Phe Ser Cys Leu Pro 143	Lys Leu Leu Tyr 142 Tyr	Asn Arg Tyr 140 Trp 0 Ser	Pro 139 His Glu Leu	Ser 137: Glu 0 Pro Leu Asp	Val 5 Lys Asn Ser Arg 1440
Gly Asp Pro Gln 142	Val Pro Gly Lys 141 Leu	Leu Ala 139 Arg O	Gln Tyr 1380 Ala 5 Pro	Gly 1365 Ser Thr Gly Asn Val	1350 Leu Gly Gly Leu Ile 143 Asn	Leu Cys Met Asp 141 Thr	Ser Arg Asp 140 Arg 5	Pro Leu 138: Ala Glu Leu	Ile 1370 Thr 5 Val Gln Gly	1358 Phe O Ser Cys Leu Pro 1438 Gln	Lys Leu Leu Tyr 142 Tyr	Asn Arg Tyr 140 Trp 0 Ser	Pro 139 His Glu Leu	Ser 137: Glu 0 Pro Leu Asp	Val 5 Lys Asn Ser Arg 1440 Thr
Gly Asp Pro Gln 142 Xaa	Pro Gly Lys 141 Leu 5 Ser	Leu Ala 139 Arg 0 Thr	Tyr 1380 Ala 5 Pro His	Gly 1365 Ser O Thr Gly Asn Val 144	1350 Leu 5 Gly Gly Leu 143 Asn	Leu Cys Met Asp 141 Thr O	Arg Asp 140 Arg Glu Phe	Pro Leu 138: Ala Glu Leu Thr	Ile 1370 Thr 5 Val Gln Gly His 145	Pro 143: Gln	Leu Leu Tyr 142 Tyr Asn	Asn Arg Tyr 140 Trp O Ser Ser	Pro 139 His 5 Glu Leu Val	Ser 1379 Glu O Pro Leu Asp Pro 145	Val 5 Lys Asn Ser Arg 1440 Thr
Gly Asp Pro Gln 142 Xaa	Pro Gly Lys 141 Leu 5 Ser	Leu Ala 139 Arg 0 Thr	Gln Tyr 1380 Ala 5 Pro His Tyr	Gly 1365 Ser Thr Gly Asn Val 144 Gly	1350 Leu 5 Gly Gly Leu 143 Asn	Leu Cys Met Asp 141 Thr O	Arg Asp 140 Arg Glu Phe	Pro Leu 1389 Ala Glu Leu Thr	Ile 1370 Thr Val Gln Gly His 145	Pro 143: Gln	Leu Leu Tyr 142 Tyr Asn	Asn Arg Tyr 140 Trp O Ser Ser	Pro 139 His 5 Glu Leu Val	Ser 1379 Glu 0 Pro Leu Asp Pro 145 Gly	Val 5 Lys Asn Ser Arg 1440 Thr
Gly Asp Pro Gln 142 Xaa Thr	Pro Gly Lys 141 Leu 5 Ser	Leu Ala 139 Arg 0 Thr Leu	Gln Tyr 1380 Ala 5 Pro His Tyr Pro 146	Gly 1369 Ser Thr Gly Asn Val 1440 Gly	1350 Leu Gly Gly Leu Ile 143 Asn 5	Deu Leu Cys Met Asp 141 Thr Gly Ser	Ser Arg Asp 140 Arg 5 Glu Phe	Pro Leu 138: Ala Glu Leu Thr Val 146	Ile 1370 Thr 5 Val Gln Gly His 145 Tyr	Pro 1433 Gln Trp	Lys Leu Leu Tyr 142 Tyr 5 Asn	Asn Arg Tyr 140 Trp 0 Ser Ser	Pro 139 His Glu Leu Val Thr 147	Ser 1379 Glu 0 Pro Leu Asp Pro 145 Gly	Val 5 Lys Asn Ser Arg 1440 Thr 5
Gly Asp Pro Gln 142 Xaa Thr	Pro Gly Lys 141 Leu 5 Ser	Leu Ala 139 Arg 0 Thr Leu Thr	Tyr 1380 Ala 5 Pro His Tyr Pro 146 Phe	Gly 1369 Ser Thr Gly Asn Val 1440 Gly	1350 Leu Gly Gly Leu Ile 143 Asn 5	Deu Leu Cys Met Asp 141 Thr Gly Ser	Ser Arg Asp 140 Arg 5 Glu Phe Thr	Pro Leu 138: Ala Glu Leu Thr Val 146 Glu	Ile 1370 Thr 5 Val Gln Gly His 145 Tyr	Pro 1433 Gln Trp	Lys Leu Leu Tyr 142 Tyr 5 Asn	Asn Arg Tyr 140 Trp 0 Ser Ser Thr	Pro 139 His 5 Glu Leu Val Thr 147 Leu	Ser 1379 Glu 0 Pro Leu Asp Pro 145 Gly	Val 5 Lys Asn Ser Arg 1440 Thr 5
Gly Asp Pro Gln 142: Xaa Thr	Pro Gly Lys 141 Leu Ser Ser	Leu Ala 139 Arg O Thr Leu Thr	Gln Tyr 1380 Ala 5 Pro His Tyr Pro 146 Phe	Gly 1365 Ser Thr Gly Asn Val 144 Gly O	1350 Leu Gly Gly Leu Ile 143 Asn 5 Thr	Leu Cys Met Asp 141 Thr Gly Ser	Arg Asp 140 Arg 5 Glu Phe Thr 148	Pro Leu 1389 Ala Glu Leu Thr Val 146 Glu	Ile 1370 Thr Val Gln Gly His 145 Tyr 5	Pro 1433 Gln Gly	Lys Leu Leu Tyr 142 Tyr 5 Asn Ala	Asn Arg Tyr 140 Trp 0 Ser Ser Thr	Pro 1390 His 5 Glu Leu Val Thr 147 Leu 5	Ser 137: Glu 0 Pro Leu Asp Pro 145 Gly 0	Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr
Gly Asp Pro Gln 142: Xaa Thr	Val Pro Gly Lys 141 Leu 5 Ser Ser Ser	Leu Ala 139 Arg 0 Thr Leu Thr Ser 147 Phe	Gln Tyr 1380 Ala 5 Pro His Tyr Pro 146 Phe	Gly 1365 Ser Thr Gly Asn Val 144 Gly O	1350 Leu Gly Gly Leu Ile 143 Asn 5 Thr	Leu Cys Met Asp 141 Thr Gly Ser His	Arg Asp 140 Arg Glu Phe Thr 148 Thr	Pro Leu 1389 Ala Glu Leu Thr Val 146 Glu	Ile 1370 Thr Val Gln Gly His 145 Tyr 5	Pro 1433 Gln Gly	Leu Leu Tyr 142 Tyr Asn Ala Pro	Asn Arg Tyr 140 Trp O Ser Ser Thr Leu 148 Glu	Pro 1390 His 5 Glu Leu Val Thr 147 Leu 5	Ser 137: Glu 0 Pro Leu Asp Pro 145 Gly 0	Val 5 Lys Asn Ser Arg 1440 Thr 5
Gly Asp Pro Gln 142: Xaa Thr Pro	Val Pro Gly Lys 141 Leu 5 Ser Ser Ser	Leu Ala 139 Arg O Thr Leu Thr Ser 147 Phe	Gln Tyr 1380 Ala 5 Pro His Tyr Pro 146 Phe 5 Asn	Gly 1365 Ser Thr Gly Asn Val 144 Gly O Pro	1350 Leu 5 Gly Gly Leu 11e 143 Asn 5 Thr Gly	Leu Cys Met Asp 141 Thr O Gly Ser His Ile	Arg Asp 140 Arg 5 Glu Phe Thr 148 Thr	Pro Leu 1389 Ala Glu Leu Thr Val 146 Glu O Asn	Ile 1370 Thr Val Gln Gly His 145 Tyr Pro	Pro 1433 Gln Gly His	Lys Leu Leu Tyr 142 Tyr Asn Ala Pro	Asn Arg Tyr 140 Trp 0 Ser Thr Leu 148 Glu 0	Pro 139 His 5 Glu Leu Val Thr 147 Leu 5	Ser 137: Glu 0 Pro Leu Asp Pro 145 Gly 0 Ile	Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr
Gly Asp Pro Gln 142 Xaa Thr Pro Phe Gln	Pro Gly Lys 141 Leu 5 Ser Ser Thr 149 His	Leu Ala 139 Arg O Thr Leu Thr Ser 147 Phe	Gln Tyr 1380 Ala 5 Pro His Tyr Pro 146 Phe 5 Asn	Gly 1365 Ser Thr Gly Asn Val 144 Gly O Pro	1350 Leu 5 Gly Gly Leu 11e 143 Asn 5 Thr Gly Thr	Leu Cys Met Asp 141 Thr O Gly Ser His Ile 149 Lys	Arg Asp 140 Arg 5 Glu Phe Thr 148 Thr	Pro Leu 1389 Ala Glu Leu Thr Val 146 Glu O Asn	Ile 1370 Thr Val Gln Gly His 145 Tyr Pro	Pro 1433 Gln Gly His	Leu Leu Tyr 142 Tyr Asn Ala Pro Tyr 150 Glu	Asn Arg Tyr 140 Trp 0 Ser Thr Leu 148 Glu 0	Pro 139 His 5 Glu Leu Val Thr 147 Leu 5	Ser 137: Glu 0 Pro Leu Asp Pro 145 Gly 0 Ile	Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr Pro
Gly Asp Pro Gln 142: Xaa Thr Pro Phe Gln 150	Pro Gly Lys 141: Leu 5 Ser Ser Ser Thr 149 His	Leu Ala 139 Arg 0 Thr Leu Thr Ser 147 Phe 0 Pro	Gln Tyr 1380 Ala 5 Pro His Tyr Pro 146 Phe 5 Asn	Gly 1365 Ser Thr Gly Asn Val 144 Gly Pro Phe	1350 Leu 5 Gly Gly Leu 11e 143 Asn 5 Thr Gly Thr	Leu Cys Met Asp 141 Thr O Gly Ser His 149 Lys	Arg Asp 140 Arg 5 Glu Phe Thr 148 Thr 5 Phe	Pro Leu 1389 Ala Glu Leu Thr Val 146 Glu Asn	Ile 1370 Thr Val Gln Gly His 145 Tyr Pro Leu	Pro 1433 Gln Gly His	Leu Leu Tyr 142 Tyr Asn Ala Pro Tyr 150 Glu	Asn Arg Tyr 140 Trp 0 Ser Thr Leu 148 Glu 0 Arg	Pro 139 His 5 Glu Leu Val Thr 147 Leu 5 Glu Val	Ser 137: Glu 0 Pro Leu Asp Pro 145 Gly 0 Ile Asn Leu	Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr Pro Met
Gly Asp Pro Gln 142: Xaa Thr Pro Phe Gln 150	Pro Gly Lys 141: Leu 5 Ser Ser Ser Thr 149 His	Leu Ala 139 Arg 0 Thr Leu Thr Ser 147 Phe 0 Pro	Gln Tyr 1380 Ala 5 Pro His Tyr Pro 146 Phe 5 Asn	Gly 1365 Ser Thr Gly Asn Val 1444 Gly Pro Phe Ser	1350 Leu 5 Gly Gly Leu 11e 143 Asn 5 Thr Gly Thr Arg 151 Leu	Leu Cys Met Asp 141 Thr O Gly Ser His 149 Lys	Arg Asp 140 Arg 5 Glu Phe Thr 148 Thr 5 Phe	Pro Leu 1389 Ala Glu Leu Thr Val 146 Glu Asn	Ile 1370 Thr Val Gln Gly His 145 Tyr Pro Leu Thr	Pro 1433 Gln O Trp Gly His Thr 151 Ser	Leu Leu Tyr 142 Tyr Asn Ala Pro Tyr 150 Glu	Asn Arg Tyr 140 Trp 0 Ser Thr Leu 148 Glu 0 Arg	Pro 139 His 5 Glu Leu Val Thr 147 Leu 5 Glu Val	Ser 1379 Glu Pro Leu Asp Pro 145 Gly Ule Asn Leu	Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr Pro Met Gln 1520 Tyr
Gly Asp Pro Gln 142: Xaa Thr Pro Phe Gln 150 Gly	Pro Gly Lys 141 Leu Ser Ser Thr 149 His Leu	Leu Ala 139 Arg O Thr Leu Thr Ser 147 Phe O Pro	Gln Tyr 1380 Ala 5 Pro His Tyr Pro 146 Phe 5 Asn Gly	Gly 1365 Ser Thr Gly Asn Val 144 Gly Pro Phe Ser Pro	1350 Leu 5 Gly Gly Leu 11e 143 Asn 5 Thr Gly Thr Arg 151 Leu 5	Leu Cys Met Asp 141 Thr O Gly Ser His 149 Lys O	Arg Asp 140 Arg 5 Glu Phe Thr 148 Thr 5 Phe Lys	Pro Leu 1389 Ala Glu Leu Thr Val 146 Glu Asn Asn	Ile 1370 Thr Val Gln Gly His 145 Tyr Pro Leu Thr	Pro 1433 Gln O Trp Gly His Thr 151 Ser 0	Lys Leu Tyr 142 Tyr Asn Ala Pro Glu 5 Val	Asn Arg Tyr 140 Trp 0 Ser Ser Thr Leu 148 Glu 0 Arg	Pro 139 His 5 Glu Leu Val Thr 147 Leu 5 Glu Val	Ser 137: Glu 0 Pro Leu Asp Pro 145 Gly 0 Ile Asn Leu 153	Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr Pro Met Gln 1520 Tyr
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Gly Asp Pro Gln 142: Xaa Thr Pro Phe Gln 150 Gly Ser	Pro Gly Lys 141 Leu Ser Ser Thr 149 His Leu Gly	Leu Ala 139 Arg O Thr Leu Thr Ser 147 Phe O Pro Leu Cys	Gln Tyr 1380 Ala 5 Pro His Tyr Pro 146 Phe 5 Asn Gly Thr Arg	Gly 1365 Ser Thr Gly Asn Val 144 Gly Pro Phe Ser Pro 152 Leu	1350 Leu 5 Gly Gly Leu 11e 143 Asn 5 Thr Gly Thr Arg 151 Leu 5	Leu Cys Met Asp 141 Thr Gly Ser His 149 Lys Phe	Arg Asp 140 Arg 5 Glu Phe Thr 148 Thr 5 Phe Lys	Pro Leu 1389 Ala Glu Leu Thr Val 146 Glu Asn Asn Arg	Ile 1370 Thr Val Gln Gly His 145 Tyr Pro Leu Thr 153 Pro	Pro 1433 Gln O Trp Gly His Ser O Glu	Lys Leu Tyr 142 Tyr Asn Ala Pro Glu 5 Val	Asn Arg Tyr 140 Trp 0 Ser Ser Thr Leu 148 Glu 0 Arg Gly	Pro 139 His 5 Glu Leu Val Thr 147 Leu 5 Glu Val Pro	Ser 137: Glu 0 Pro Leu Asp Pro 145 Gly 0 Ile Asn Leu 153 Ala	Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr Pro Met Gln 1520 Tyr

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Trp Glu 18: Leu Le:	18' u Lei 90 u Asj	ı Asp 75 ı Sei p Arg	50 Pro Lys Gly	Lev Lev Ser	Asn Thr 189	Pro 188 Cys 5 Tyr	Gly 0 Gly Val	Gly 5 Leu Ile Asr	Val Asp 11e 16l 191	Arg Glu 190 y Phe	g Glu 188 1 Leu 00 e Thi	Ile 187 Gln 55 Gly	Cys 0 Leu Pro	Thr Tyr Tyr Asn 1920
Trp Glo 18: Leu Le	18' u Lei 90 u Asj	ı Asp 75 ı Sei p Arg	50 Pro Lys g Gly	Leu Ser 191 Ser Ser	Asn Thr 189	Pro 188 Cys 5 Tyr	Gly 0 Gly Val	Gly 5 Lev Ile Asr	Val Asp 11e 11f 19f r Ser	Arg Glu 190 y Phe	g Glu 188 1 Leu 00 e Thi	Ile 187 Gln 55 Gly	Cys 0 Leu Pro	Thr Tyr Tyr Asn 1920
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Trp Glu 18: Leu Le 1905 Phe Va	18° u Le 90 u Asj l Pr r Gl u Va	n Asp 75 n Sen p Arc o Ile u The 19 1 Pre	50 Pro Lys Gly Thi 193 C Pro	Lev Ser 191 Ser 25 Ser	Asn 189 Leu 10 Thr	Pro 188 Cys 5 Tyr Pro	Gly Gly Val Gly Fro 194	Gly 5 Lev 11e Asr 193 Arc	Value Asp e Ile e Ile n Gly 193 r Ses 30 g Pre	e Glu 190 y Phe 15 r Thi	g Glu 188 n Leu 00 e Thi r Val e Val	Ile 187 Gln S5 Gly His His Pro 195	Cys 0 Leu Pro Arg 193 Gly	Thr Tyr Tyr Asn 1920 Gly 35
Trp Glu 18: Leu Le 1905 Phe Va Thr Se	18' u Le 90 u As l Pr r Gl u Va	n Asp 75 n Sen p Arg o Ile u Thi 19 1 Pre	50 Pro Lys Gly Thi 193 Pro 40 O Pho	Lev Ser 191 Ser Ser 25 Ser	Asn 189 Leu 10 Thr	Pro 188 Cys 5 Tyr Pro Leu Asn	Gly Cal Gly Gly Fro 194 Pro 196	Gly 5 Leu Ile Asr 193 Aro	Val Asp Elle 191 193 r Ses 30 g Pro	e Glu 190 y Phe 15 r Thi o Ile	y Glu 188 1 Leu 20 2 Thi 1 Val 2 Val 3 T Asi 199	Ile 187 Gln S5 Gly His His L Pro 195 n Let	Cys 0 Leu Pro Arg 193 Gly 60	Thr Tyr Tyr Asn 1920 Gly 35 Pro
Trp Gla 18: Leu Le 1905 Phe Va Thr Se Leu Le Glu Gl	18' u Le 90 u As l Pr r Gl u Va 19 u Al	n Asp 75 n Sen p Arg o Ile u Thi 19 1 Pre	50 Pro Lys Gly Thi 193 Pro 40 O Pho	Lev Ser 191 Ser Ser 25 Ser	Asn 1 Thr 189 1 Leu 10 10 Thr Ser 1 Leu	Pro 188 Cys 5 Tyr Pro Leu 196 Gly	Gly Cal Gly Gly Fro 194 Pro 196	Gly 5 Leu Ile Asr 193 Aro	Val Asp Elle 191 193 r Ses 30 g Pro	e Glu 190 y Phe 15 r Thi o Ile	Glu 188 1 Lev 200 e Thi r Val e Val r Asi 196 e Asi	Ile 187 Gln S5 Gly His His L Pro 195 n Let	Cys 0 Leu Pro Arg 193 Gly 60	Thr Tyr Tyr Asn 1920 Gly 35 Pro
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Trp Glu 18: Leu Leu 1905 Phe Va Thr Se Leu Le Glu Gl 19 Arg Va	18" u Let 90 u As; l Pr r Gl u Va 19 u Al	a Asp 75 a Sea o Ile o Ile u Tha 19 1 Pro 55 a Me	50 Pro Lys J Gly Thi 193 C Pro 40 O Pho	Lev Ser 191 Ser Ser Ser Thr His	Asn 189 Leu 10 Thr Ser Leu 197 u Leu	Pro 188 Cys 5 Tyr Pro Leu 1 Asn 196 5 Gly	Gly OGly Val Gly Pro 194 Phe	Gly 5 Leu Ile Asr Thi 193 Arc	Value Aspending Aspending Programmer Communication Communi	e Gluy Phe 190 y Phe 15 r Thi o Ilo e Thi	Glu 188 1 Leu 00 2 Thi 2 Val 2 Val 2 Asi 4 Asi 6 Asi 80	Ile 187 Gln 55 Gly His L His L Pro 195 n Let	Cys 0 Leu Pro Arg 193 0 Gly 50 1 Glr	Thr Tyr Tyr Asn 1920 Gly Fro Tyr Glu Tr
Trp Glu 18: Leu Leu 1905 Phe Va Thr Se Leu Le Glu Gl 19 Arg Va	18" u Le 90 u As 1 Pr r Gl u Va 19 u Al 70	n Asp 75 n Ser p Arg o Ile u Th: 19 1 Pr 55 a Me	50 Pro Lys g Gly 193 r Pro 40 o Pho t Ar	Jeung His	Asn 189 Leu 10 Thr Ser Leu 197 u Leu	Pro 188 Cys 5 Tyr Pro Leu 1 Asn 196 5 Gly	Gly Cly Val Gly From 194 Pro 194 Phe	Gly 5 Leu 11e Asr 193 Arg 15 Thi Arg	Value Aspending Property of the Lagrange Prope	o Arc 190 y Phe 15 r Thi o Ile e Thi s Phe 19 e Ly	y Glu 188 n Leu 00 e Thi r Val e Val e Asi 80 s Asi	His Gly His His Pro 195 n Let 65 n Tha	Cys 0 Leu Pro Arg 193 0 Gly 100 1 Glr	Thr Tyr Tyr 1920 1 Gly 35 7 Pro 1 Tyr c Glu r Ile 2000
Trp Glu 18: Leu Leu 1905 Phe Va Thr Se Leu Le Glu Gl 19 Arg Va 1985 Gly Pr	18" u Lee 90 u As r Gl u Va 19 u Al 70 l Lee	n Asp 75 n Ser p Arg o Ile u Th: 19r 55 a Me	50 Pro Lys g Gly 193 r Pro 40 o Pho t Ar n Gl r Se	y Lev 191 1 Ser 25 25 25 Ser 25 26 Thr 191 191 191 191	Asn 189 Leu 10 Thr Ser Leu 197 u Leu 90	Pro 188 Cys 5 Tyr Pro Leu 1 Asn 196 0 Gly 15 1 Arg	Gly Cly Val Gly Pro 194 Phe	Gly 5 Leu 11c Asr 7 Thi 193 6 Arc 6 Thi 20 Leu 1 Th. 20	Value Aspending Properties 19:10 Propert	e Glu 190 y Phe 15 r Thi o Ilo e Th: 19 e Ly 95	y Glu 188 1 Leu 00 e Thi r Val e Val e Asi 80 s Asi	His I Gly I Gly I His I Pro 195 I Leu 65 In Tha	Cys 0 Leu Pro Arg 193 0 Gly 100 1 Thi r Sei 201	Thr Tyr Tyr 1920 1 Gly 35 7 Pro 1 Tyr Clu 1 Clu 2000 1 Lys 15
Trp Glu 18: Leu Leu 1905 Phe Va Thr Se Leu Le Glu Gl 19 Arg Va	18" u Lee 90 u As r Gl u Va 19 u Al 70 l Lee	n Asp 75 n Ser p Arg o Ile u Th: 19r 55 a Me	50 Pro Lys g Gly 193 r Pro 40 o Pho t Ar n Gl r Se	y Lev 191 1 Ser 25 25 25 Ser 25 26 Thr 191 191 191 191	Asn 189 Leu 10 Thr Ser Leu 197 u Leu 90	Pro 188 Cys 5 Tyr Pro Leu 1 Asn 196 0 Gly 15 1 Arg	Gly Cly Val Gly Pro 194 Phe	Gly 5 Leu 11c Asr 7 Thi 193 6 Arc 6 Thi 20 Leu 1 Th. 20	Value Aspending Properties 19:10 Propert	e Glu 190 y Phe 15 r Thi o Ilo e Th: 19 e Ly 95	y Glu 188 1 Leu 00 e Thi r Val e Val e Asi 80 s Asi	His I Gly I Gly I His I Pro 195 I Leu 65 In Tha	Cys 0 Leu Pro Arg 193 0 Gly 100 1 Thi r Sei 201	Thr Tyr Tyr 1920 1 Gly 35 7 Pro 1 Tyr Clu 1 Clu 2000 1 Lys 15



								2225					2020		
			2020)		_	_	2025		_	-	m	2030		Cor
		2035					2040	Glu)				2045)		
	2050	Thr	His			2055	,	Leu			2060)			
2065					2070)		Thr		2075	5				2080
Thr	Ser			2085	5			Val	2090)				2095)
			2100)				Ala 2105	;				2110)	
		2115					2120					2125)		
_	2130)				2135	5	Asn			2140)			
2145	5				2150)		Ser		215	5				2160
				2165	5			Arg	2170)				2175	•
			2180)				His 2185	5				2190	,	
_		2195	5				220					220	5		
	2210)				221	5	Thr			222)			
	_	Gly	Phe	Thr			Ser	Ser	vaı	223	TIIT	TIIT	ser	1117	2240
2225 Gly	Thr	Phe	Thr			Pro	Glu	Thr	Ser 225	Glu		Pro	Ser	Ser 225	Leu
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Phe	Thr	Ile 227	Ile	Asn	Leu	Gln	Tyr 228	Glu		Asp	Met	His 228	Arg		Gly
	229	Lys 0	Phe			229	Glu 5	Arg			230	Gly O	Leu		
230	5				231	0		Ser		231	5				2320
				232	5			Asp	233	0				233	5
			234	0				Pro 234	5				235	U	
		235	5				236	Gln 0				236	5		
	237	0				237	5	His			238	0			
238	5				239	0		Thr		239	5				2400
				240	5			Pro	241	0				241	5
			242	0				Phe 242	5				243	0	
		243	5				244					244	5		
	245	0				245	5	Gly			246	0			
246	5				247	0				247	'5				Leu 2480
Arg	Pro	Lys	Lys	Asp	Gly	Ala	Ala	Thr	Lys	. Val	. Asp	Ala	Ile	Cys	Thr

2490 2485 Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln Leu Tyr 2500 2505 Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro Tyr 2525 2515 2520 Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr Gln Arg Ser 2540 2530 2535 Ser Val Pro Thr Thr Ser Ile Pro Gly Thr Pro Thr Val Asp Leu Gly 2550 2555 Thr Ser Gly Thr Pro Val Ser Lys Pro Gly Pro Ser Ala Ala Ser Pro 2570 2565 Leu Leu Val Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr 2590 2580 2585 Glu Glu Asn Met Gln His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu 2605 2595 2600 Arg Val Leu Gln Gly Leu Leu Arg Ser Leu Phe Lys Ser Thr Ser Val 2620 2610 2615 Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys 2625 2630 2635 Asp Gly Thr Ala Thr Gly Val Asp Ala Ile Cys Thr His His Pro Asp 2650 2645 Pro Lys Ser Pro Arg Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser 2665 2670 2660 Gln Leu Thr His Asn Ile Thr Glu Leu Gly Xaa Tyr Ala Leu Asp Asn 2680 2685 Asp Ser Leu Phe Val Asn Gly Phe Thr His Arg Ser Ser Val Ser Thr 2690 2695 2700 Thr Ser Thr Pro Gly Thr Pro Thr Val Tyr Leu Gly Ala Ser Lys Thr 2705 2710 2715 Pro Ala Ser Ile Phe Gly Pro Ser Ala Ala Ser His Leu Leu Ile Leu 2725 2730 Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met 2740 2745 2750 Trp Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly 2765 2755 2760 Leu Leu Arg Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser 2770 2775 2780 Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr 2795 2790 Gly Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Thr Gly Pro Gly 2810 2805 Leu Asp Arg Glu Gln Leu Tyr Leu Glu Leu Ser Gln Leu Thr His Ser 2825 2830 2820 Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val 2845 2840 2835 Asn Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val 2855 2860 Val Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg 2875 2880 2870 Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr 2890 2895 2885 Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser 2905 2910 2900 Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser Val 2925 2920 Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu Gln 2940 2935 Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu Leu

				0055		2960
2945	29	50	3 Tou	2955	Tur Sar	-
Ser Gln Gln '	2065		297	70		2313
Lys Asp Ser	2980		2985		233	,
Pro Pro Thr		300	0		3005	
Glu Ala Thr		3015		3020		
Phe Thr Ile	30	30		3035		3040
Ala Thr Phe	3045		30:	50		3033
Leu Phe Gln	3060		3065		307	U
Ile Ser Leu 3075		308	80		3085	
Thr Cys Thr 3090		3095		3100)	
Gln Leu Tyr 3105	31	10		3115		2120
Gly Phe Tyr	3125		21.	30		3133
Pro Gln Asn	3140		3145		272	U
Val Asn Trp 3155	.	316	0		2702	
Thr Leu Leu 3170		3175		3180	J	
Ser Gln Leu 3185	٦.	190		3195		3200
Met Asp Ser	3205		32	10		3213
Asp Pro Ser	3220		3225		323	i U
Ser Phe His 3235	5	324	40		3243	
Thr Glu Met 3250		3255		326	U	
Gln His Phe 3265	3	270		3275		3280
Asp Lys Ala	3285		32	90		3295
Ile Glu Asp	3300		3305		333	LU
Tyr Phe Ser	5	33	20		3325	
His His Thr 3330		3335		334	0	
Arg Val Asp 3345	3	350		3355		2300
Asn Gly Thr	3365		33	370		3313
Val Asp Gly	3380		3385		33	90
Asp Leu Pro 339	5	34	00		3405	
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3445 3450

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Pro Thr Ala Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

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